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(71) Applicants and
(72) Inventors: **TONKS, Nicholas, K.** [GB/US]; 3 Arrowhead Place, Huntington, NY 11743 (US). **BARFORD, David** [GB/GB]; 58 Redcliffe Square, London SW10 9BN (GB). **NEEL, Benjamin, G.** [US/US]; 7 Grove Street, Wayland, MA 01778 (US). **FLINT, Andrew, J.** [US/US]; 22925 49th Avenue SE, Bothell, WA 98021 (US).

(74) Agents: **ROSOK, Mae, Joanne** et al.; Seed Intellectual Property Law Group PLLC, Suite 6300, 701 Fifth Avenue, Seattle, WA 98104-7092 (US).

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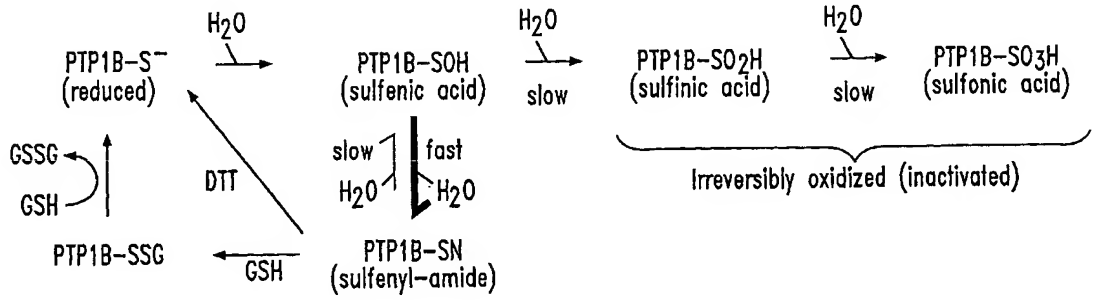
(54) Title: NOVEL FORM OF PROTEIN TYROSINE PHOSPHATASES AND METHODS FOR IDENTIFYING MOLECULES BINDING THERETO



(57) Abstract: The invention relates to novel forms of protein tyrosine phosphatase enzymes and methods of using such enzymes to identify agents or compounds capable of altering or modulating the activity of the native protein tyrosine phosphatase.

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NOVEL FORM OF PROTEIN TYROSINE PHOSPHATASES AND METHODS FOR IDENTIFYING MOLECULES BINDING THERETO

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Patent Application No. 60/476,036 filed June 4, 2003, which is incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

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TECHNICAL FIELD

The present invention relates to the protein tyrosine phosphatase family of enzymes that mediate biological signal transduction, and in particular to novel forms of such phosphatases, and to assays using such novel protein tyrosine phosphatases.

BACKGROUND OF THE INVENTION

Reversible protein tyrosine phosphorylation, coordinated by the actions of protein tyrosine kinases (PTKs) that phosphorylate certain tyrosine residues in polypeptides, and of protein tyrosine phosphatases ("PTPs") that dephosphorylate certain phosphotyrosine residues, is a key mechanism in regulating many cellular activities. It is becoming apparent that the diversity and complexity of the PTPs and PTKs are comparable, and that PTPs are equally important in delivering both positive and negative signals for proper function of cellular machinery. Regulated tyrosine phosphorylation contributes to

specific pathways for biological signal transduction, including those associated with cell division, proliferation and differentiation. Defects and/or malfunctions in these pathways may underlie certain disease conditions for which effective means for intervention remain elusive, including for example, malignancy, autoimmune disorders, diabetes, obesity and infection.

The protein tyrosine phosphatase family of enzymes consists of approximately 100 structurally diverse gene products that have in common a highly conserved amino acid PTP catalytic domain, but which display considerable variation in their non-catalytic segments. In particular, the "classical" PTPs, exclusively catalyze dephosphorylation of (and thus exhibit specificity for) phosphotyrosine residues in phosphoproteins and phosphopeptides, in contrast to the "dual specificity phosphatase" (DSP), members of the PTP family that are capable of dephosphorylating phosphotyrosine as well as phosphoserine and phosphothreonine residues in substrate phosphopolypeptides. This structural diversity presumably reflects the diversity of physiological roles of individual PTP family members, which in certain cases have been demonstrated to have specific functions in growth, development and differentiation (Desai et al., 1996 *Cell 84*:599-609; Kishihara et al., 1993 *Cell 74*:143-156; Perkins et al., 1992 *Cell 70*:225-236; Pingel and Thomas, 1989 *Cell 58*:1055-1065; Schultz et al., 1993 *Cell 73*:1445-1454). PTPs participate in a variety of physiologic functions, providing a number of opportunities for therapeutic intervention in physiologic processes through alteration or modulation (*e.g.*, statistically significant up-regulation or down-regulation) of PTP activity.

Although recent studies have also generated considerable information regarding the structure, expression and regulation of PTPs, the identities of some of the tyrosine-phosphorylated substrates through which the PTPs exert their effects remain to be determined. Studies with a limited number of synthetic phosphopeptide substrates have demonstrated some differences in the substrate selectivity of different PTPs (Cho et al., 1993 *Protein Sci.* 2: 977-984; Dechert et al., 1995 *Eur. J. Biochem.* 231:673-681; Ramachandran et al., *Biochemistry* 31:4232-38 (1992)). Analyses of PTP-mediated dephosphorylation of PTP substrates suggest that catalytic activity may be favored by the

presence of certain amino acid residues at specific positions in the substrate polypeptide relative to the phosphorylated tyrosine residue (Ruzzene et al., 1993 *Eur. J. Biochem.* 211:289-295; Zhang et al., 1994 *Biochemistry* 33:2285-2290). Thus, although the physiological relevance of the substrates used in these studies is unclear, PTPs display a certain level of substrate selectivity *in vitro*. The family of PTPs can be subdivided into two categories: the classical PTPs, which comprise phosphotyrosine (pTyr)-specific enzymes typified by PTP1B and CD45, and the dual specificity phosphatases ("DSPs") which dephosphorylate pSer/pThr as well as pTyr residues. The DSPs largely maintain the same catalytic mechanism as the classical PTPs and have been implicated in a wide range of fundamentally important signaling events from control of MAP kinases in cell proliferation to the regulation of cyclin dependent kinases in the cell cycle.

The PTP signature motif (Cys-$(X)_5$-R) (SEQ ID NO:1) is invariant among all PTPs. The cysteine residue in this motif is invariant in members of the family and is known to be essential for catalysis of the phosphotyrosine dephosphorylation reaction. This cysteine functions as a nucleophile to attack the phosphate moiety present on a phosphorylated amino acid residue (*e.g.*, phosphotyrosine, and/or pSer/pThr in the case of a DSP) of the incoming substrate.

For some PTPs, mutation of the catalytic cysteine residue results in a "substrate trapping" mutant PTP that is catalytically deficient but retains the ability to complex with, or bind to, its substrate, at least *in vitro*. (*e.g.*, Sun et al., 1993 *Cell* 75:487). Such signature sequence cysteine mutants of certain other PTP family members, however, do not form stable complexes with substrate. In order to derive catalytically deficient, substrate trapping mutants of such PTPs, instead of substituting serine for cysteine in the CX_5R (SEQ ID NO:1) motif, a wildtype protein tyrosine phosphatase catalytic domain invariant aspartate residue is replaced with an amino acid that does not cause significant alteration of the Km of the enzyme but that results in a reduction in Kcat, as disclosed, for example, in U.S. Patent Nos. 5,912,138 and 5,951,979, in U.S. Application No. 09/323,426, and in PCT/US97/13016 and PCT/US00/14211. (See also, *e.g.*, Flint et al., 1997 *Proc. Natl. Acad. Sci.* 94:1680). Substrates of other PTPs can be

identified using similar substrate trapping mutant PTPs, for example, substrates of the PTP family members PTP-PEST (Garton et al., 1996 *J. Mol. Cell. Biol.* 16:6408), TCPTP (Tiganis et al., 1998 *Mol. Cell Biol.* 18:1622), PTP-HSCF (Spencer et al., 1997 *J. Cell Biol.* 138:845), and PTP-H1 (Zhang et al., 1999 *J. Biol. Chem.* 274:17806).

Mitogen-activated protein kinases (MAP-kinases, MAPK) are components of conserved cellular signal transduction pathways that have a variety of conserved members and that that are integral to the cell's response to stimuli such as growth factors, hormones, cytokines, and environmental stresses. MAP-kinases are activated via phosphorylation by MAP-kinase kinases at a dual phosphorylation motif that is present in MAPK and that has the sequence Thr-X-Tyr, in which phosphorylation at both the tyrosine and threonine residues is required for MAPK activity. Activated MAP-kinases phosphorylate several signal transduction targets, including effector protein kinases and transcription factors. Inactivation of MAP-kinases is mediated by dephosphorylation of the MAPK Thr-X-Tyr site by dual-specificity phosphatases referred to as MAP-kinase phosphatases. In higher eukaryotes, the physiological role of MAP-kinase signaling has been correlated with cellular events such as proliferation, oncogenesis, development, and differentiation. Accordingly, the ability to regulate signal transduction via these pathways could lead to the development of treatments and preventive therapies for human diseases associated with MAP-kinase signaling, such as cancer.

Dual-specificity protein tyrosine phosphatases (dual-specificity phosphatases, or "DSPs"), as stated above, dephosphorylate both phosphotyrosine and phosphothreonine/phosphoserine residues on a variety of substrates (Walton et al., *Ann. Rev. Biochem.* 62:101-120, 1993), including mitogen-activated protein kinases (MAP-kinases, MAPK). MAPKs are a family of conserved cellular signal transduction pathway members that that are integral to cellular responses to physiological stimuli (*e.g.*, growth factors, hormones, cytokines, environmental stresses, etc.). More than 50 dual-specificity phosphatases that dephosphorylate and inactivate a MAP-kinase have been identified (Shen et al., *Proc. Natl. Acad. Sci. USA* 98:13613-18 (2001); *see also, e.g.*, U.S. Patent Nos. 6,492,157 and 6,551,810), including MKP-1 (WO 97/00315; Keyse and Emslie,

Nature 59:644-647 (1992)); MKP-2 (WO97/00315); MKP-4, MKP-5, MKP-7, Hb5 (WO 97/06245); PAC1 (Ward et al., *Nature* 367:651-654 (1994)); HVH2 (Guan and Butch, *J. Biol. Chem.* 270:7197-7203 (1995)); and PYST1 (Groom et al., *EMBO J.* 15:3621-3632 (1996)). These dual-specificity phosphatases differ in expression, tissue and subcellular distribution, and specificity for MAP-kinase family members. Expression of certain dual-specificity phosphatases is induced by stress or mitogens, but others appear to be expressed constitutively in specific cell types. The regulation of dual-specificity phosphatase expression and activity is considered to be significant in the control of MAP-kinase mediated cellular functions, including cell proliferation, cell differentiation and cell survival. For example, dual-specificity phosphatases may function as negative regulators of cell proliferation. Very likely, many such dual-specificity phosphatases exist, having varying specificities with regard to cell type or activation state.

In contrast to the role of most dual-specificity phosphatases in the inactivation (*i.e.*, down-regulation) of MAP-kinases, one DSP enzyme, herein referred to as JSP-1 (Jun kinase Stimulating Phosphatase-1) or dual-specificity phosphatase 3 (DSP-3), has been reported to have the capability to function as a selective activator of the JNK MAP-kinase signaling pathway (Shen et al., *supra*; WO 01/21812). DSP-3 appears also to affect the activity of other kinases involved in the JNK pathway (Shen et al., *supra*; WO 01/21812). For example, overexpression of DSP-3 leads to activation of MKK4, a MAP-kinase kinase that functions upstream of JNK (Shen et al., *supra*; Lawler et al., *Curr. Biol.* 8:1387-90 (1998); Yang et al., *Proc. Natl. Acad. Sci. USA* 94: 3004-3009 (1997)).

Activation of JNK is believed to be involved in several physiological processes, including embryonic morphogenesis, cell survival, and apoptosis. A number of JNK signaling pathway substrates have been identified, including c-Jun, ATF2, ELK-1 and others. JNK signaling has also been associated with various disease conditions, such as tumor development, ischemia and reperfusion injury, diabetes, hyperglycemia-induced apoptosis, cardiac hypertrophy, inflammation, and neurodegenerative disorders.

Hence, and as also noted above, over the last fifteen years it has been established that the PTPs are a large, structurally diverse family whose members exhibit exquisite substrate specificity *in vivo* and act as important regulators of a wide array of cellular signaling pathways (Andersen et al., 2001 *Mol. Cell. Biol.* 21:7117; Tonks and Neel, 2001 *Curr. Opin. Cell Biol.* 13:182). An important area of investigation in the field remains the characterization of mechanisms by which the activities of the PTPs themselves may be regulated *in vivo*.

Recently, the art has understood that certain PTPs may be susceptible to site-specific oxidation and consequent inactivation, introducing an additional tier of complexity to the regulation of this family of enzymes. It is now apparent that reactive oxygen species (ROS) are not merely a harmful by-product of life in an aerobic environment. The importance of ROS in physiological activities mediated by phagocytic cells, such as neutrophils, is well documented. Various stimuli lead to the assembly of a multi-component NADPH oxidase complex, which mediates a process known as the respiratory burst (DeLeo et al., 1996 *J. Leukoc. Biol.* 60:677). NADPH oxidase catalyses transfer of one electron from NADPH to molecular oxygen to generate superoxide anions, which in turn may yield hydrogen peroxide, either via protonation of superoxide or through the action of superoxide dismutase (Thelen et al., 1993 *Physiol. Rev.* 73:797). The large quantities of such ROS that are produced in phagocytic cells have been implicated as microbiocidal agents and in certain pathological situations can result in host cell damage (Smith et al., 1991 *Blood* 77:673). However, many recent studies have revealed that the production of ROS is tightly regulated, engendering the concept that, at lower levels than those generated for a microbiocidal function, ROS may also function in propagating a signaling response to extracellular stimuli (Finkel, 1998 *Curr. Opin. Cell Biol.* 10:248; Finkel, 2000 *FEBS Lett.* 476:52). Thus, in a manner analogous to reversible protein phosphorylation, the reversible oxidation of target proteins in a cell may regulate the function of those proteins in response to various agonists and thus elicit a cellular response to stimulation (Finkel, 1998).

Several lines of investigation have implicated ROS in the regulation of mitogenic signaling in mammalian cells (Adler et al., 1999 *Oncogene* 18:6104; Brummel et al., 1996 *J. Biol. Chem.* 271:1455-61; Chen et al., 1995 *J. Biol. Chem.* 270:28499; Sundaresan et al., 1995 *Science* 270:296). Mild oxidation can yield a stable sulfenic acid modification of cysteine residues (Cys-SOH) in selected proteins, including a variety of enzymes and transcription factors, which modification has the potential to regulate the function of those proteins (Claiborne et al., 1999 *Biochemistry* 38:15407). In order to understand the role of ROS and redox regulation in the control of signal transduction, it is particularly important to identify the targets of reversible oxidation *in vivo*. In this context, attention has been drawn to the PTPs, which together with the PTKs are responsible for maintaining a normal protein tyrosine phosphorylation status *in vivo*.

The PTPs are cysteine-dependent enzymes that possess the signature motif, -Cys-$(X)_5$-Arg- (SEQ ID NO:1), which forms the base of the active site cleft and contains an invariant cysteine residue (Barford et al., 1995 *Nat. Struct. Biol.* 2:1043). The PTP catalytic dephosphorylation mechanism involves a two-step process, commencing with nucleophilic attack by the Sγ atom of the PTP catalytic site cysteine on the phosphorus atom of the phosphotyrosyl substrate, resulting in formation of a phospho-cysteine intermediate. In the second step the transient phospho-enzyme intermediate is hydrolyzed by an activated water molecule (Barford et al., 1995). Due to the unusual environment of the PTP active site, the pKa of the sulfhydryl group of this cysteine residue is extremely low (~5.4 in PTP1B, (Lohse et al., 1997 *Biochemistry* 36:4568) and ~4.7 in YOP, (Zhang et al., 1993 *Biochemistry* 32:9340)) compared to the typical pKa for Cys (~8.5); this low pKa of the PTP active site cysteine favors its function as a nucleophile but renders it susceptible to oxidation. It has now been shown *in vitro* that treatment with hydrogen peroxide (H_2O_2) of various PTPs (Lee et al., 1998 *J. Biol. Chem.* 273:15366), including dual specificity phosphatases (Denu et al., 1998 *Biochemistry* 37:5633) and low molecular weight PTPs (Caselli et al., 1998 *J. Biol. Chem.* 273:32554), leads to oxidation of the active site cysteine to sulfenic acid. Such oxidation results in

inhibition of activity because the modified cysteine can no longer function as a phosphate acceptor in the first step of the PTP-catalyzed reaction.

Hydrogen peroxide (H_2O_2) is a natural cellular second messenger produced in response to hormones, growth factors and cytokines, and is required for the optimal activation of numerous signal transduction pathways, particularly those mediated by protein tyrosine kinases (Finkel, *Curr. Opin. Cell Biol.* 10:248-53 (1998); Finkel, *Dev. Cell* 2:251-59 (2002); Rhee et al., *Sci. STKE* 53 (2000); available at Internet:http://www.stke.org/cgi/content/full/OC_sigtrans;2000/53/pel); Sundaresan et al., *Science* 270:296-99 (1995); Rao, *Oncogene* 13:713-19 (1996); Bae et al., *J. Biol. Chem.* 272:217-21 (1997); Knebel et al., *EMBO J.* 15:5314-25 (1996)). One mechanism by which H_2O_2 regulates cellular processes is to transiently inhibit PTPs by reversibly oxidizing their catalytic site cysteine residues, thereby suppressing protein dephosphorylation (Knebel et al., *supra*; Mahadev et al., *J. Biol. Chem.* 276:21938-42 (2001); Lee et al., *J. Biol. Chem.* 273:15366-72 (1998)). Oxidation of such cysteine to sulfenic acid is reversible (Claiborne et al., 1999 *Biochemistry* 38:15407), and thus has the potential to form the basis of a mechanism for reversible regulation of PTP activity. In contrast, oxidation by the addition of two (sulfinic acid) or three (sulfonic acid) oxygens to the active site cysteine is irreversible. Interestingly, glutathionylation of the sulfenic acid form of PTP1B has been reported (Barrett et al., 1999 *Biochemistry* 38:6699) and is proposed as a mechanism to protect against further irreversible oxidation and as an important step in the reverse reduction mechanism. Stimulation of A431 cells with EGF was also shown to lead to the production of H_2O_2 and concomitant inhibition of PTP1B (Bae et al., 1997 *J. Biol. Chem.* 272:217). Increased production of intracellular oxidants may therefore contribute to enhanced, tyrosine phosphorylation-dependent signaling, for example in response to growth factors (Bae et al., 1997; Bae et al., 2000 *J. Biol. Chem.* 275:10527; Sundaresan et al., 1995 *Science* 270:296), by transiently suppressing the enzymatic activity of members of the PTP family, thereby promoting a burst of PTK activity (Finkel, 1998; 2000, *supra*).

One non-transmembrane, or intracellular, PTP, PTP1B, recognizes several tyrosine-phosphorylated proteins as substrates, many of which are involved in human disease. For example, therapeutic inhibition of PTP1B in the insulin-signaling pathway may serve to augment insulin action, thereby ameliorating the state of insulin resistance common in Type II diabetes patients. PTP1B acts as a negative regulator of signaling that is initiated by several growth factor/ hormone receptor PTKs, including p210 Bcr-Abl (LaMontagne et al., *Mol. Cell. Biol.* 18:2965-75 (1998); LaMontagne et al., *Proc. Natl. Acad. Sci. USA* 95:14094-99 (1998)), receptor tyrosine kinases, such as EGF receptor, PDGF receptor, and insulin receptor (IR) (Tonks et al., *Curr. Opin. Cell Biol.* 13:182-95 (2001)), and JAK family members such as Jak2 and others (Myers et al., *J. Biol. Chem.* 276:47771-74 (2001)), as well as signaling events induced by cytokines (Tonks and Neel, 2001). Activity of PTP1B is regulated by modifications of several amino acid residues in the polypeptide, such as phosphorylation of Ser residues (Brautigan and Pinault, 1993; Dadke et al., 2001; Flint et al., 1993), and oxidation of the active Cys residue in its catalytic motif (Lee et al., 1998; Meng et al., 2002), which is evolutionarily conserved among protein tyrosine phosphatases and dual phosphatase family members (Andersen et al., 2001).

Diabetes mellitus is a common, degenerative disease affecting 5-10% of the human population in developed countries, and in many countries, it may be one of the five leading causes of death. Approximately 2% of the world's population has diabetes, the overwhelming majority of cases (>97%) being type 2 diabetes and the remainder being type 1. In type 1 diabetes, which is frequently diagnosed in children or young adults, insulin production by pancreatic islet beta cells is destroyed. Type 2 diabetes, or "late onset" or "adult onset" diabetes, is a complex metabolic disorder in which cells and tissues cannot effectively use available insulin; in some cases insulin production is also inadequate. At the cellular level, the degenerative phenotype that may be characteristic of late onset diabetes mellitus includes, for example, impaired insulin secretion and decreased insulin sensitivity, *i.e.*, an impaired response to insulin.

Studies have shown that diabetes mellitus may be preceded by or is associated with certain related disorders. For example, an estimated forty million individuals in the U.S. suffer from late onset impaired glucose tolerance (IGT). Patients with IGT fail to respond to glucose with increased insulin secretion. Each year a small percentage (5-10%) of individuals with IGT progress to insulin deficient non-insulin dependent diabetes mellitus (NIDDM). NIDDM and IDDM are associated with decreased release of insulin by pancreatic beta cells and/or a decreased response to insulin by cells and tissues that normally exhibit insulin sensitivity. Other symptoms of diabetes mellitus and conditions that precede or are associated with diabetes mellitus include obesity, vascular pathologies, and various neuropathies, including blindness and deafness.

Type 1 diabetes is treated with lifelong insulin therapy, which is often associated with undesirable side effects such as weight gain and an increased risk of hypoglycemia. Current therapies for type 2 diabetes (NIDDM) include altered diet, exercise therapy, and pharmacological intervention with injected insulin or oral agents that are designed to lower blood glucose levels. Examples of such presently available oral agents include sulfonylureas, biguanides, thiazolidinediones, repaglinide, and acarbose, each of which alters insulin and/or glucose levels. None of the current pharmacological therapies, however, controls the disease over its full course, nor do any of the current therapies correct all of the physiological abnormalities in type 2 NIDDM, such as impaired insulin secretion, insulin resistance, and excessive hepatic glucose output. In addition, treatment failures are common with these agents, such that multi-drug therapy is frequently necessary.

In certain metabolic diseases or disorders, one or more biochemical processes, which may be either anabolic or catabolic (*e.g.*, build-up or breakdown of substances, respectively), are altered (*e.g.*, increased or decreased in a statistically significant manner) or modulated (*e.g.*, up- or down-regulated to a statistically significant degree) relative to the levels at which they occur in a disease-free or normal subject such as an appropriate control individual. The alteration may result from an increase or decrease in a substrate, enzyme, cofactor, or any other component in any biochemical

reaction involved in a particular process. Altered (*i.e.*, increased or decreased in a statistically significant manner relative to a normal state) PTP activity can underlie certain disorders and suggests a PTP role in certain metabolic diseases.

For example, disruption of the murine PTP1B gene homolog in a knock-out mouse model results in $PTP1B^{-/-}$ mice exhibiting enhanced insulin sensitivity, decreased levels of circulating insulin and glucose, and resistance to weight gain even on a high-fat diet, relative to control animals having at least one functional PTP1B gene (Elchebly et al., *Science* 283:1544 (1999)). Insulin receptor hyperphosphorylation has also been detected in certain tissues of PTP1B deficient mice, consistent with a PTP1B contribution to the physiologic regulation of insulin and glucose metabolism (*id.*). PTP1B-deficient mice exhibit decreased adiposity (reduced fat cell mass but not fat cell number), increased basal metabolic rate and energy expenditure, and enhanced insulin-stimulated glucose utilization (Klaman et al., 2000 *Mol. Cell. Biol.* 20:5479). Additionally, altered PTP1B activity has been correlated with impaired glucose metabolism in other biological systems (*e.g.*, McGuire et al., *Diabetes* 40:939 (1991); Myerovitch et al., *J. Clin. Invest.* 84:976 (1989); Sredy et al., *Metabolism* 44:1074 (1995)), including PTP1B involvement in biological signal transduction via the insulin receptor (*see, e.g.*, WO 99/46268 and references cited therein).

An integration of crystallographic, kinetic, and PTP1B-peptide binding assays illustrated the interaction of PTP1B and insulin receptor (IR) (Salmeen et al., *Mol. Cell* 6:1401-12 (2000)). The insulin receptor (IR) comprises two extracellular α subunits and two transmembrane β subunits. Activation of the receptor results in autophosphorylation of tyrosine residues in both β subunits, each of which contains a protein kinase domain. Extensive interactions that form between PTP1B and insulin receptor kinase (IRK) encompass tandem pTyr residues at 1162 and 1163 of IRK, such that pTyr-1162 is brought into close proximity with the active site of PTP1B (*id.*). The presence in IRK of the Asp/Glu-pTyr-pTyr-Arg/Lys (SEQ ID NO:22) motif has been implicated for optimal recognition by PTP1B of IRK. This motif is also present in other receptor PTKs, including Trk, FGFR, and Axl. In addition, this motif is found in the JAK family of

PTKs, members of which transmit signals from cytokine receptors, including a classic cytokine receptor that is recognized by the satiety hormone leptin (Touw et al., *Mol. Cell. Endocrinol.* 160:1-9 (2000)).

Changes in the expression levels of PTP1B have been observed in several human diseases, particularly in diseases associated with disruption of the normal patterns of tyrosine phosphorylation. For example, the expression of PTP1B is induced specifically by the p210 Bcr-Abl oncoprotein, a PTK that is directly responsible for the initial manifestations of chronic myelogenous leukemia (CML) (LaMontagne et al., *Mol. Cell. Biol.* 18:2965-75 (1998); LaMontagne et al., *Proc. Natl. Acad. Sci. USA* 95:14094-99 (1998); Fukada et al., *EMBO J.* 22:479 (2003)). Expression of PTP1B in response to this oncoprotein is regulated, in part, by transcription factors Sp1, Sp3, and Egr-1 (Fukada et al., *J. Biol. Chem.* 276:25512-19 (2001)). These transcription factors have been shown to bind to a p210 Bcr-Abl responsive sequence (PRS) in the human *PTP1B* promoter, located between 49 to 37 base pairs from the transcription start site, but they do not appear to mediate certain additional, independent PTP1B transcriptional events, for which neither transcription factor(s) nor transcription factor recognition element(s) have been defined (*id.*). An enhancer sequence within the PTP1B promoter serves as a binding site for the transciption factor Y box-binding protein-1 (YB-1), which also regulates expression of PTP1B (Fukada and Tonks, *EMBO J.* 22:479-93 (2003)). A correlation was observed between the expression of PTP1B and that of YB-1 in cancer cell lines and in an animal model of type II diabetes (*id.*).

Currently, therefore, desirable goals for therapeutic regulation of biological signal transduction include modulation of PTP-mediated cellular events including, *inter alia*, inhibition or potentiation of interactions among PTP-binding molecules, substrates and binding partners, or other agents that regulate PTP activities. Accordingly, a need exists in the art for an improved ability to intervene in the regulation of phosphotyrosine signaling, including regulating PTPs by altering PTP catalytic activity (preventing or substantially preventing the reversibility of an oxidative event that results in oxidized PTP), and/or by altering PTP binding to PTP substrate molecules, and/or by

altering PTP-encoding gene expression. An increased ability to so regulate PTPs may facilitate the development of methods for modulating the activity of proteins involved in phosphotyrosine signaling pathways and for treating conditions associated with such pathways.

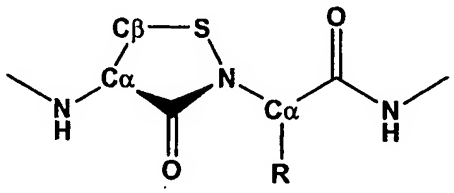
Presently, a number of screening assays for agents that regulate PTP activities are known, yet each of these assays has significant limitations, for example, with respect to specificity, sensitivity, or speed. Similarly, poor specificity for PTPs is a shortcoming of certain assays known to the art that, through the use of fluorescence, detect catalytic dephosphorylation of hydrolyzable phosphorylated substrates. Such fluorescence assays employ phosphate esters of fluorescein, for example OMFP (3-O-methylfluorescein phosphate, *e.g.,* Gottlin et al., 1996 *J. Biol. Chem.* 271:27445) or FDP (fluorescein diphosphate, *e.g.,* Huyer et al., 1997 *J. Biol. Chem.* 272:843). These detectable substrates are intrinsically unstable in solution, however, making them poorly suitable for high throughput screening applications. Moreover, PTPs exhibit high specificity for phosphotyrosyl peptide substrates, as noted above, while showing poor specificity for unnatural organic phosphate esters such as OMFP or FDP. Such assays therefore suffer from unreliability due to detection of spurious phosphate group hydrolysis by contaminating phosphatases that are not PTPs, and/or inefficient hydrolysis by PTPs of the artificial organic phosphate ester substrates.

Another type of PTP assay employs substrates for which PTPs have high specificity, such as tyrosine phosphorylated proteins or peptides. These assays detect PTP activity by monitoring the release of free phosphate following PTP hydrolysis of such substrates. These assays are time-consuming and expensive, and involve additional procedural measures related to the storage, handling and disposal of radioactive materials.

Clearly a need exists for improved reagents and assays for identifying agents that modulate dephosphorylation processes. The present invention fulfills these needs and further provides other related advantages.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides an isolated polypeptide comprising the amino acid sequence –C-$(X)_5$-R- (SEQ ID NO:1), wherein C is cysteine, R is arginine, and X is any amino acid residue, and wherein a sulfur atom of the cysteine is covalently linked to a main-chain nitrogen atom of an adjacent C-terminal amino acid residue; an isolated protein tyrosine phosphatase polypeptide in a cyclic sulfenyl-amide form (PTP-SN); and an isolated polypeptide comprising the sequence -Cys-$(X)_5$-Arg- (SEQ ID NO:1), wherein X is any amino acid residue, and wherein the cysteine residue and the adjacent C-terminal amino acid residue in SEQ ID NO:1 form the following chemical structure



wherein R is the amino acid side chain of the adjacent C-terminal amino acid residue. In certain embodiments, the polypeptide is PTP1B comprising the amino acid sequence set forth in any one of SEQ ID NOS:24, 26, and 30; cdc14a comprising the amino acid sequence set forth in any one of SEQ ID NOS:85, 87, and 89; cdc14b comprising the amino acid sequence set forth in any one of SEQ ID NOS:91 and 93; cdc25a comprising the amino acid sequence set forth in any one of SEQ ID NOS:67 and 69; cdc25b comprising the amino acid sequence set forth in any one of SEQ ID NOS:77 and 79; cdc25c comprising the amino acid sequence set forth in any one of SEQ ID NOS:81 and 83; DSP-3/JSP-1 comprising the amino acid sequence set forth in SEQ ID NO:97; or DEP-1 comprising the amino acid sequence set forth in any one of SEQ ID NOS:38 and 40.

In another embodiment, the invention provides an isolated protein tyrosine phosphatase (PTP) enzyme comprising a sequence [I/V]HCXAGXXR[S/T]G (SEQ ID NO:106), wherein X is any amino acid, and wherein cysteine in SEQ ID NO:106 and the

adjacent C-terminal residue together form a cyclic sulfenyl-amide group between the sulfur atom of the cysteine and the main-chain nitrogen atom of the adjacent C-terminal residue. In particular embodiments, the PTP is (a) PTP1B comprising the amino acid sequence set forth in any one of SEQ ID NOS:24, 26, and 30 or (b) DEP-1 comprising the amino acid sequence set forth in any one of SEQ ID NOS:38 and 40.

The invention also provides a method of making a protein tyrosine phosphatase in a cyclic sulfenyl-amide form (PTP-SN) comprising subjecting a biological sample comprising a PTP that comprises the sequence C-$(X)_5$-R (SEQ ID NO:1), wherein X is any amino acid, to oxidation conditions for a time and under conditions sufficient to induce the cysteine residue of SEQ ID NO:1 to form a cyclic sulfenyl-amide with the adjacent C-terminal residue.

Also provided by the present invention is a method for identifying a compound that hinders reduction of a cyclic sulfenyl-amide protein tyrosine phosphatase (PTP-SN) comprising (a) introducing a PTP-SN to a test compound to form a composition; (b) adding a reducing agent to the composition of (a) under conditions and for a time sufficient to permit binding of the test compound to the PTP-SN; and (c) analyzing the composition to determine the presence or absence of PTP-SN. In certain embodiments, the reducing agent is beta-mercaptoethanol, dithiothreitol (DTT), dithioerythritol (DTE), glutathione, or a phosphine. In another embodiment, the step of analyzing comprises performing a functional assay on the composition to determine PTP catalytic activity. In a particular embodiment, the compound stabilizes the PTP-SN in the oxidized state. In one embodiment, the PTP is PTP1B comprising the amino acid sequence set forth in any one of SEQ ID NOS:24, 26, and 30; cdc14a comprising the amino acid sequence set forth in any one of SEQ ID NOS:85, 87, and 89; cdc14b comprising the amino acid sequence set forth in any one of SEQ ID NOS:91 and 93; cdc25a comprising the amino acid sequence set forth in any one of SEQ ID NOS:67 and 69; cdc25b comprising the amino acid sequence set forth in any one of SEQ ID NOS:77 and 79; cdc25c comprising the amino acid sequence set forth in any one of SEQ ID NOS:81 and 83; DSP-3/JSP-1 comprising the

amino acid sequence set forth in SEQ ID NO:97; or DEP-1 comprising the amino acid sequence set forth in any one of SEQ ID NOS:38 and 40.

In another embodiment, the invention provides a method for identifying a compound that binds to a protein tyrosine phosphatase sulfenyl-amide form (PTP-SN) comprising (a) contacting a PTP-SN with a test compound; and (b) determining binding of the compound to the PTP-SN, thereby identifying a compound that binds to the PTP-SN. In certain embodiments, the compound does not bind to a PTP-SN that has been converted to a catalytically active PTP by reducing conditions. In a particular embodiment, the step of determining binding comprises performing X-ray crystallographic analysis. In another particular embodiment, the compound stabilizes the PTP-SN in the oxidized state. In one embodiment, the PTP is PTP1B comprising the amino acid sequence set forth in any one of SEQ ID NOS:24, 26, and 30; cdc14a comprising the amino acid sequence set forth in any one of SEQ ID NOS:85, 87, and 89; cdc14b comprising the amino acid sequence set forth in any one of SEQ ID NOS:91 and 93; cdc25a comprising the amino acid sequence set forth in any one of SEQ ID NOS:67 and 69; cdc25b comprising the amino acid sequence set forth in any one of SEQ ID NOS:77 and 79; cdc25c comprising the amino acid sequence set forth in any one of SEQ ID NOS:81 and 83; DSP-3/JSP-1 comprising the amino acid sequence set forth in SEQ ID NO:97; or DEP-1 comprising the amino acid sequence set forth in any one of SEQ ID NOS:38 and 40.

In another embodiment, a method is provided for identifying a compound that modulates or hinders reduction of a cyclic sulfenyl-amide protein tyrosine phosphase-1B (PTP1B-SN) comprising: (a) obtaining crystalline PTP1B-SN; (b) introducing a test compound to the crystalline PTP1B-SN under conditions and for a time sufficient to permit binding of the test compound to the PTP1B-SN; and (c) analyzing the crystalline PTP1B-SN to determine whether the test compound binds thereto. In another specific embodiment, the invention provides a method for identifying a compound that hinders reduction of a cyclic sulfenyl-amide protein tyrosine phosphase-1B (PTP1B-SN) comprising: (a) introducing a test compound to the PTP1B-SN to form a composition; (b) adding a reducing agent to the composition of (a), under conditions and for a time sufficient to

permit binding of the test compound to the PTP1B-SN; and analyzing the composition to determine the presence or absence of PTP1B-SN.

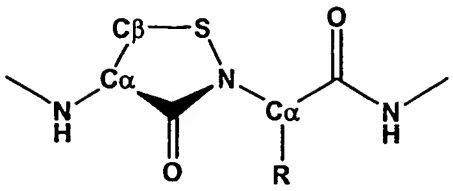
The invention also provides a double mutant protein tyrosine phosphatase (PTP) polypeptide having the amino acid sequence $-CS(X)_4-R-$ set forth in SEQ ID NO:109, wherein X is any amino acid, said mutant PTP comprising a substitution of the cysteine in SEQ ID NO:1 and a substitution of the amino acid that is the adjacent C-terminal residue to the cysteine residue. In a particular embodiment, the catalytic domain of the double mutant PTP possesses a three-dimensional structure that is substantially similar to the three-dimensional structure of the catalytic domain of the corresponding PTP-SN. In certain embodiments, the cysteine residue is substituted with an alanine residue and/or the adjacent C-terminal residue is substituted with an alanine residue.

In another embodiment, the invention provides a double mutant protein tyrosine phosphatase (PTP) polypeptide having the amino acid sequence -H-C-S-X-G-X-G-R-X-G- set forth in SEQ ID NO:21, wherein X is any amino acid, and the mutant PTP comprises (a) a substitution of the cysteine in SEQ ID NO:21, and (b) a substitution of the serine that is adjacent to the cysteine residue. In a particular embodiment, the catalytic domain of the double mutant PTP possesses a three-dimensional structure that is substantially similar to the three-dimensional structure of the catalytic domain of the corresponding PTP-SN.. In certain particular embodiments, the double mutant PTP polypeptide is PTP1B comprising the amino acid sequence set forth in any one of SEQ ID NOS:24, 26, and 30 or DEP-1 comprising the amino acid sequence set forth in any one of SEQ ID NO:38 and 40.

The invention also provides a double mutant protein tyrosine phosphatase-1B (PTP1B) polypeptide comprising the amino acid sequence of SEQ ID NO:109 in which the cysteine in SEQ ID NO:109 is substituted and the serine in SEQ ID NO:109 is substituted, wherein the cysteine is located at position number 215 in any one of SEQ ID NOS:24, 26, and 30 and the serine is located at position number 216 in any one of SEQ ID NOS:24, 26, and 30, and wherein the double mutant PTP1B is at least 80% identical, at least 90% identical, at least 95% identical, or at least 99% identical to the amino acid

sequence set forth in in any one of SEQ ID NOS:24, 26, and 30. In a particular embodiment, the cysteine located at position 215 is substituted with a alanine residue, and the serine located at position 216 is substituted with an alanine residue. In another particular embodiment, the double mutant PTP comprises the amino acid sequence set forth in SEQ ID NO:110.

In another embodiment, the invention provides an antibody, or an antigen-binding fragment thereof, that binds to at least one polypeptide selected from (a) a double mutant protein tyrosine phosphatase (PTP) polypeptide having the amino acid sequence –$CS(X)_4$-R- set forth in SEQ ID NO:109, wherein X is any amino acid, and wherein the mutant PTP comprises a substitution of the cysteine in SEQ ID NO:1 and a substitution of an amino acid that is an adjacent C-terminal residue to the cysteine residue; wherein the catalytic domain of the double mutant PTP possesses a three-dimensional structure that is substantially similar to the three-dimensional structure of the catalytic domain of the corresponding PTP-SN; (b) a double mutant protein tyrosine phosphatase (PTP) polypeptide having the amino acid sequence -H-C-S-X-G-X-G-R-X-G- set forth in SEQ ID NO:21, wherein X is any amino acid, and wherein the mutant PTP comprises (1) a substitution of the cysteine in SEQ ID NO:21, and (2) a substitution of serine that is adjacent to the cysteine residue; wherein the catalytic domain of the double mutant PTP possesses a three-dimensional structure that is substantially similar to the three-dimensional structure of the catalytic domain of the corresponding PTP-SN; (c) a PTP-SN polypeptide comprising comprising the amino acid sequence –C-$(X)_5$-R- (SEQ ID NO:1), wherein C is cysteine, R is arginine, and X is any amino acid residue, and wherein a sulfur atom of the cysteine is covalently linked to a main-chain nitrogen atom of an adjacent C-terminal amino acid residue; or (d) a PTP-SN polypeptide comprising the sequence Cys-$(X)_5$-Arg (SEQ ID NO:1), wherein X is any amino acid residue, and wherein the cysteine residue and an adjacent C-terminal amino acid residue in SEQ ID NO:1 form the following chemical structure



wherein R is the amino acid side chain of the adjacent C-terminal amino acid residue. In another embodiment, the antibody or antigen binding fragment thereof binds to at least two polypeptides. In another particular embodiment, the antibody or antigen binding fragment thereof binds to at least one double mutant PTP polypeptide and to at least one PTP-SN polypeptide. In certain embodiments the antibody is a polyclonal antibody or a monoclonal antibody. The monoclonal antibody is a mouse monoclonal antibody, a human monoclonal antibody, a rat monoclonal antibody, or a hamster monoclonal antibody. In another embodiment, the antigen-binding fragment is a Fab, a Fab', a $F(ab')_2$, a Fv, or a Fd fragment. The antibody may be a chimeric antibody, a humanized antibody, or a single chain antibody. The invention also provides a hybridoma that produces the monoclonal antibody and also provides a host cell that expresses an antibody or an antigen-binding fragment thereof. In another embodiment, the invention provides such antibody or antibody fragment and a physiological carrier.

In another embodiment, the invention provides a method for identifying an agent that binds specifically to a double mutant protein tyrosine phosphatase (PTP) polypeptide comprising (a) contacting a double mutant PTP as described herein (having the amino acid sequence $-CS(X)_4-R-$ set forth in SEQ ID NO:109, wherein X is any amino acid, said mutant PTP comprising a substitution of the cysteine in SEQ ID NO:1 and a substitution of the amino acid that is the adjacent C-terminal residue to the cysteine residue or a double mutant protein tyrosine phosphatase (PTP) polypeptide having the amino acid sequence -H-C-S-X-G-X-G-R-X-G- set forth in SEQ ID NO:21, wherein X is any amino acid, and the mutant PTP comprises a substitution of the cysteine in SEQ ID NO:21 and a substitution of the serine that is adjacent to the cysteine residue) with a candidate agent under conditions and for a time sufficient to permit interaction between the mutant PTP and the candidate agent; (b) contacting the corresponding wildtype PTP polypeptide with the

candidate agent under conditions and for a time sufficient to permit interaction between the wildtype PTP and the candidate agent; (c) comparing the level of binding of the candidate agent to the mutant PTP with the level of binding of the candidate agent to the wildtype PTP, wherein an increased level of binding to the mutant PTP relative to the level of binding to the wildtype PTP indicates that the agent specifically binds to the mutant PTP polypeptide.

In another embodiment, a method is provided for identifying an agent that alters reduction of a protein tyrosine phosphatase sulfenyl-amide form (PTP-SN) comprising: (a) contacting a double mutant PTP polypeptide as described herein with a candidate agent under conditions and for a time sufficient to permit interaction between the mutant PTP and the candidate agent; (b) contacting the corresponding wildtype PTP polypeptide with the candidate agent under conditions and for a time sufficient to permit interaction between the wildtype PTP and the candidate agent; (c) determining a level of binding of the candidate agent to the mutant PTP; (d) determining a level of binding of the candidate agent to the wildtype PTP; and (e) comparing the level of binding of the candidate agent to the mutant PTP relative to the level of binding of the candidate agent to the wildtype PTP, wherein an increased or decreased level of binding of the candidate agent to the mutant PTP indicates that the agent alters reduction of a PTP-SN. The double mutant PTP has the amino acid sequence –$CS(X)_4$-R- set forth in SEQ ID NO:109, wherein X is any amino acid, and wherein the mutant PTP comprises a substitution of the cysteine in SEQ ID NO:1 and a substitution of the amino acid that is the adjacent C-terminal residue to the cysteine residue. In another embodiment, the double mutant protein tyrosine phosphatase (PTP) polypeptide having the amino acid sequence -H-C-S-X-G-X-G-R-X-G- set forth in SEQ ID NO:21, wherein X is any amino acid, and the mutant PTP comprises a substitution of the cysteine in SEQ ID NO:21 and a substitution of the serine that is adjacent to the cysteine residue.

These and other aspects of the invention will become evident upon reference to the following detailed description and attached drawings. In addition,

various references to published documents are set forth herein which describe in more detail certain aspects of this invention, and are therefore incorporated by reference in their entireties.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Figure 1 presents electron density maps showing that the oxidation of PTP1B resulted in formation of a sulfenyl-amide bond between the thiol Cys215 and the amide nitrogen of Ser216. Figure 1A is a stereo view of the electron density map of the PTP loop in the sulfenyl-amide structure, which was calculated using 2*Fo-Fc*, *Fo-Fc*, and -|*Fo-Fc*| Fourier coefficients. The closed arrowhead and open arrowhead correspond to electron densities calculated using *Fo-Fc*, and -|*Fo-Fc*| Fourier coefficients, respectively. The *Fo-Fc* electron density indicated that no oxygen atoms were attached to the Cys215 sulfur atom, but that a small amount of the enzyme was still reduced. Figure 1B presents electron density maps (2*Fo-Fc*) showing the time-dependent changes at the catalytic Cys215 of PTP1B by oxidation for six time points over a 16-hour period. At 40 and 75 minutes a mixture of reduced and oxidized (sulfenyl-amide) states were present. In Figure 1B, (red) = reduced state; (red+ox) = reduced plus oxidized states; (ox) = oxidized state; (SO_2/SO_3) = mixture of sulfinic and sulfonic acid states. Figures were drawn using PYMOL (*see* Internet:http://pymol.sourceforge.net/).

Figure 2 shows the conformational changes accompanying oxidation of PTP1B. Figure 2A presents a ribbons diagram showing the catalytic site of reduced PTP1B. Figure 2B shows the sulfenyl-amide species of PTP1B in the same orientation as reduced PTP1B in Figure 2A. Figure 2C illustrates superimposition of reduced and sulfenyl-amide states of PTP1B. The view has been rotated relative to the diagrams presented in Figure 2A and 2B for clarity. In the figure, "(red)" = reduced and "(ox)" = oxidized. Figures were drawn using PYMOL (*see* Internet:http://pymol.sourceforge.net/). Figure 2D illustrates the chemical mechanism for generation of the sulfenyl-amide bond. "X:" denotes a nucleophile.

Figure 3 shows a pulse-chase analysis of oxidation of PTP1B in solution. Figure 3A represents SDS-PAGE gels of wild-type PTP1B (top left) and the substrate trapping mutant C215S PTP1B (top right) incubated with increasing concentrations of H_2O_2 and the corresponding MALDI mass spectra for the Cys215- and Ser216-containing peptides after trypsinolysis (bottom panel). At high concentrations of $H_2{}^{16}O_2$ (10^3 and 10^4 μM), irreversible oxidation was accompanied by a shift in the mass of the active site peptide of 32 and 48 dalton (Da) (corresponding to the addition of two or three oxygens). Irreversible oxidation was also accompanied by retardation in electrophoretic mobility of the protein observed on SDS PAGE. No change in molecular weight (M_r) was observed for the equivalent peptide from the PTP1B-C215S control at any concentration of H_2O_2 tested (right). Figure 3B shows inhibition of PTP1B catalytic activity by $H_2{}^{18}O_2$. Enzymatically active PTP1B was incubated with increasing amounts of $H_2{}^{18}O_2$ for 30 minutes at room temperature and then divided into 3 aliquots. One aliquot was assayed for enzyme activity, and another was assayed for reversibility of oxidation. A third aliquot was incubated for 2 hours with greater than 100-fold excess of $H_2{}^{16}O_2$. The molecular weights of the tryptic digest active site peptides were determined. For each concentration of H_2O_2, activity is shown in the left panel and the equivalent MALDI mass spectrum is shown on the right. At concentrations of $H_2{}^{18}O_2$ up to 320 μM, inhibition of enzyme activity was reversible with approximately 90% of enzyme activity recovered upon reactivation. At high concentrations of $H_2{}^{18}O_2$ or $H_2{}^{16}O_2$ (50 mM), oxidation and inactivation were irreversible and yielded the sulfonic acid (Cys-SO_3) derivative with an increase in peptide mass of +54 and +48 Da, respectively. Under conditions of reversible oxidation in the presence of $H_2{}^{18}O_2$, which would not oxidize the Cys residue beyond the sulfenic acid (Cys-SO) form, followed by a chase with excess $H_2{}^{16}O_2$, the sulfonic acid derivative produced displayed an increased mass of +48 (3 atoms of ^{16}O). No sulfonic acid derivative was detected that displayed an increase in mass of +50 (1 atom of ^{18}O and 2 atoms of ^{16}O) although the mass resolution of the technique (+/- 0.3 Da) was sufficient for its detection.

Figure 4 illustrates the effects of oxidation on substrate binding and phosphorylation of PTP1B. Figure 4A illustrates the inter-relationship of PTP1B redox species. The reaction mechanism presented shows that in response to H_2O_2, Cys215 is oxidized to sulfenic acid and activity is inhibited. Rapid reaction of sulfenic acid with the amide of Ser216 eliminates water, generating the sulfenyl-amide species, which by reacting with thiols generates mixed disulfide intermediates and reduction of the enzyme, returning it to an active state. In a competing reaction, sulfenic acid is oxidized to the irreversible sulfinic and sulfonic acids in a process that could be accelerated by high concentrations of H_2O_2 and strong oxidizing agents, *e.g.*, pervanadate. Figure 4B: Examination of the effects of oxidation on binding of the insulin receptor kinase (IRK) by a substrate trapping mutant form of PTP1B (D181A PTP1B). PTP1B was immunoprecipitated with antibody FG6, and the PTP1B immunoprecipitates were immunoblotted with anti-pTyr antibodies (upper panel) and an anti-IRK antibody (middle panel), which revealed that increasing concentrations of H_2O_2 led to disruption of a PTP1B/IR complex, and that tyrosyl phosphorylation of PTP1B by the IRK was enhanced at higher concentrations of H_2O_2. Ponceau S staining of the filter confirmed that an equal amount of PTP1B was immunoprecipitated from each sample (lower panel). Figure 4C: Mutation of Tyr46 in PTP1B led to attenuation of oxidation induced phosphorylation of the PTP by the insulin receptor kinase. Tyrosyl phosphorylation of PTP mutants PTP1B D181A and PTP1B D181A/Y46F in the IR kinase assay described above, are compared in the autoradiograph (48 hour exposure, upper panel). The lower panel shows the Coomassie blue stained gel.

Figure 5 shows the structural relationships between cysteine thiol, cysteine sulfenic acid, and cysteine sulfenyl amide.

Figure 6 presents the sequence alignment of classical PTPs with the signature motif –C-$(X)_5$-R- (SEQ ID NO:1), which is illustrated at the bottom.

Figure 7 shows the sequence alignment of dual specificity phosphatases with the signature motif –C-$(X)_5$-R- illustrated at the bottom.

Figure 8 shows the sulfenyl-amide species reduced to SH using either DTT or glutathione. Figure 8(A) presents the electron density map of Cys215 in the sulfenyl-amide state before reduction. Figure 8(B) illustrates the electron density map after incubation with DTT, and Figure 8(C) shows the electron density map after reduction by glutathione, in which the SH state was recovered. The sulfenyl-amide species eventually oxidized to the irreversible Cys-SO_3 state after 3 months as illustrated in Figure 8(D), which was identical in conformation to pervanadate-induced oxidation of PTP1B, shown as a stereoview in Figure 8(E).

Figure 9 shows the Nano-flow electrospray spectra of reduced PTP1B, Mr 37310.74±0.24 Da (Figure 9A) and oxidized PTP1B, Mr 37309.2±0.18 Da (Figure 9B). A mass difference of 1.5 Da was observed. The theoretical mass of the PTP1B construct is 37312.6 Da. On formation of the sulfenyl-amide species a loss of 2 Da (loss of protons from -SH of Cys 215 and NH of Ser 216 (uncharged PTP1B)) was expected.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to the surprising discovery that when a protein tyrosine phosphatase (PTP) is oxidized, a sulfenic acid intermediate is produced and is rapidly converted into a previously unknown form, namely a sulfenyl-amide species, wherein the sulfur atom of the catalytic cysteine is covalently linked to the polypeptide backbone nitrogen atom of the amino acid residue situated immediately C-terminal to the cysteine, thus creating a cyclic sulfenyl-amide form. Oxidation of PTP to the cyclic sulfenyl-amide form is also accompanied by significant, or large, conformational changes in the catalytic site that effectively inhibit substrate binding. This unusual protein modification protects the active site cysteine residue of a PTP from irreversible oxidation to sulfinic acid and sulfonic acid and permits redox regulation of the enzyme by promoting its reversible reduction by thiols. As described herein, compositions and methods related to these discoveries may find a variety of uses, for instance, in drug screening (including antibody screening) and therapeutic applications whereby at least

one functionally compromised PTP-sulfenyl amide (PTP-SN) is stabilized in the sulfenyl amide form, thereby reducing the level of active PTP.

In addition, it has been discovered that the sulfur atom of the PTP catalytic cysteine can form a disulfide bond ("SS") with the sulfur atom of a conformationally-proximal or nearby cysteine residue. Such a disulfide bond effectively inactivates the PTP until such PTP-SS is exposed to appropriate reducing conditions, whereupon it may be reactivated. Such PTPs herein are designated as "PTP-SS" polypeptides (*see, e.g.*, Caselli et al., *J. Biol. Chem.* 273:32554-60 (1998); Chiarugi et al., *J. Biol. Chem.* 276:33478-87 (2001); Fauman et al., *Cell* 93: 617-625 (1998); Reynolds et al., *J. Mol. Biol.* 293: 559-568 (1999); Savitsky et al., *J. Biol. Chem.* 277: 20535-20540 (2002); Hanlon et al., *Protein Sci.* 7: 508-511 (1998); Song et al., *Mol. Cell* 7:615-626 (2001); Lee et al., *J. Biol. Chem.* 277: 20336-20342 (2002)).

In certain embodiments, the invention is directed to compositions and methods for monitoring and regulating PTP activity, including methods for identifying agents or compounds that inhibit, regulate, modulate, or alter (*e.g.*, increase or decrease with statistical significance), and preferably that decrease, the activity of a native PTP. Such compositions comprise novel, oxidized forms of PTPs, or mutated PTPs described herein below that structurally mimic, or act as a surrogate for, such oxidized PTPs. The methods described herein comprise assays useful for identifying compounds that can modulate, regulate, hinder, inhibit, or otherwise alter the reduction of the inactivated oxidized sulfenyl-amide form of the PTP. In certain preferred embodiments, agents identified by these assays are antagonists of PTP activity (*e.g.*, agents that inhibit, hinder, or decrease the activity of the PTP). The agent may be an endogenous physiological substance or may be an antibody or a natural or synthetic drug, including an organic small molecule as provided herein.

As used herein, the term "PTP" means a protein tyrosine phosphatase enzyme capable of dephosphorylating a phosphorylated tyrosine residue in a protein, polypeptide, or peptide. Such PTPs of the invention are identified by their signature catalytic cysteine motif: -C-$(X)_5$-R- (SEQ ID NO:1), wherein the cysteine residue is the

catalytic cysteine and wherein "X" can be any amino acid residue, natural or unnatural. The definition of PTP herein includes "classical" PTPs, which dephosphorylate tyrosine residues, and which have the signature motif sequence –C-S-X_4-R- (SEQ ID NO:109), for example, -H-C-S-X-G-X-G-R-X-G- (SEQ ID NO:21), wherein "X" can be any amino acid residue. Andersen et al. (*Mol. Cell. Bio.* 21:7117-7136 (2001); *FASEB J.* 18:8-30 (2004), which as also noted above are incorporated herein by reference) describe and illustrate this structural relationship among classical protein tyrosine phosphatase domains. Such classical PTPs are described, and GenBank reference numbers provided therefor, in Andersen et al. (2001 *Mol. Cell. Biol.* 21:7117) and herein.

For example, the PTP may be PTP1B (*e.g.*, GenBank Accession Nos. M31724 (SEQ ID NOS:23-24); NM_002827 (SEQ ID NOS:25-26); NM_011201 (SEQ ID NOS:27-28); M33689 (SEQ ID NOS:29-30); M33962 (SEQ ID NOS:31-32)); PTP-epsilon (*e.g.*, Genbank Accession Nos. NM_006504 (SEQ ID NOS:33-34) and NM_130435(SEQ ID NOS:35-36)); DEP-1 (CD148; PTP-eta; F-36-12) (U10886 (SEQ ID NOS:37-38); D37781 (SEQ ID NOS:39-40); AAB26475 (SEQ ID NO:41); U.S. Patent No. 6,114,140); and SEQ ID NO:159-160)); TCPTP (*e.g.*, GenBank Accession Nos. M25393 (SEQ ID NOS:163–164); NM_002828 (SEQ ID NOS:165-166; NM_080422 (SEQ ID NOS:167-168); PTPH1 (SEQ ID NO:96-97; U.S. Patent Nos. 5,595,911; 5,863,781; 6,479,640); SHP2 (*e.g.*, GenBank Accession Nos. D13540 (SEQ ID NOS:42-43); L03535 (SEQ ID NOS:44-45); L07527 (SEQ ID NOS: 46-47); X70766 (SEQ ID NOS: 48-49); L08807 (SEQ ID NO: 50); S78088 (SEQ ID NOS: 51-52); S39383 (SEQ ID NO: 53); D84372 (SEQ ID NOS: 54-55); U09307 (SEQ ID NOS: 56-57)); SHP1 (M74903 (SEQ ID NOS: 58-59); X62055 (SEQ ID NOS: 60-61); M77273 (SEQ ID NOS: 62-63); M90388 (SEQ ID NOS: 64-65); cdc25a (*e.g.*, GenBank Accession Nos. NM_001789 (SEQ ID NOS: 66-67), AF527417 (SEQ ID NOS: 68-69), NM_133571 (SEQ ID NOS: 70-71)); cdc25b (*e.g.*, GenBank Accession Nos. NM_133572 (SEQ ID NOS: 72-73), NM_023117 (SEQ ID NOS: 74-75), NM_021872 (SEQ ID NOS: 76-77); M81934 (SEQ ID NOS: 78-79); cdc25c (*e.g.*, GenBank Accession Nos. NM_001790 (SEQ ID NOS: 80-81), NM_022809 (SEQ ID NOS: 82-

83)); cdc14a (*e.g.*, GenBank Accession Nos. AF122013 (SEQ ID NOS: 84-85); AF064102 (SEQ ID NOS: 86-87); AF064103 (SEQ ID NOS: 88-89); Li et al., 1997 *J. Biol. Chem.* 272:29403; U.S. Patent No. 6,331,614); cdc14b (*e.g.*, GenBank Accession Nos. AF064104 (SEQ ID NOS: 90-91); AF064105 (SEQ ID NOS: 92-93)); DSP-2 (WO 00/56899) (SEQ ID NOS: 94-95); DSP-3 (WO 00/60092) (SEQ ID NOS:96-97); DSP-4 (U.S. Patent Publication No. 2003/175829; (SEQ ID NOS: 112-113)); DSP-5 (SEQ ID NOS: 114-115; DSP-5 alternate form (SEQ ID NOS:116-117); U.S. Patent Application No. 6,645,753;); DSP-6; DSP-7 (WO 00/60098); (SEQ ID NOS: 118-120)); DSP-8 (WO 00/63393; (SEQ ID NOS: 121-122)); DSP-9 (U.S. Patent No. 6,492,157; (SEQ ID NOS: 123-124)); DSP-10 (U.S. Patent No. 6,551,810; (SEQ ID NOS: 125-126)); DSP-11 (U.S. Patent No. 6,649,391; WO 01/05983; (SEQ ID NOS: 127-128)); DSP-12 (U.S. Patent Publication No. 2001/049358; U.S.A.N. 09/775,925; (SEQ ID NOS: 129-130)); DSP-13 (U.S. Patent Publication No. 2001/049358; U.S.A.N. 09/775,925; (SEQ ID NOS: 131-132)); DSP-14 (U.S.A.N. 09/847,519 and WO 01/46394; (SEQ ID NOS: 133-134)); DSP-15 (SEQ ID NOS: 135-136; DSP-15 alternate form (SEQ ID NOS:137-138); U.S. Patent Publication No. 2002/182203); DSP-16 (SEQ ID NOS: 139-140; DSP-16 alternate form (SEQ ID NOS:141-142); U.S. Patent Publication No. 2002/137170); DSP-17 (U.S.A.N. 10/076,859; (SEQ ID NOS: 143-144)); DSP-18 (U.S. Patent Publication No. 2003/092114; (SEQ ID NOS: 145-158)); CD45 (Charbonneau et al., *Proc. Natl. Acad. Sci. USA* 85:7182-86 (1988); Genbank Accession Nos. NM_080922 (SEQ ID NOS: 98-99), NM_080921 (SEQ ID NOS: 100-101), NM_002838 (SEQ ID NOS: 102-103), and NM_080923) (SEQ ID NOS: 104-105). Conserved amino acids may be readily found at positions in a PTP polypeptide, particularly within the signature catalytic cysteine motif and at positions proximal to the motif, toward both the amino terminus and toward the carboxy terminus of the PTP and flanking the signature motif (for example, [I/V]HCXAGXXR[S/T]G (SEQ ID NO:106). In addition to comprising the motif sequence of SEQ ID NO:1, PTPs of the invention may comprise any of the following sequences:

His-Cys-$(X)_5$-Arg	(SEQ ID NO:2)
Val-His-Cys-$(X)_5$-Arg	(SEQ ID NO:3)
Ile-His-Cys-$(X)_5$-Arg	(SEQ ID NO:4)
Cys-$(X)_5$-Arg-Ser	(SEQ ID NO:5)
Cys-$(X)_5$-Arg-Thr	(SEQ ID NO:6)
Cys-$(X)_5$-Arg-Ser-Gly	(SEQ ID NO:7)
Cys-$(X)_5$-Arg-Thr-Gly	(SEQ ID NO:8)
His-Cys-$(X)_5$-Arg-Ser	(SEQ ID NO:9)
His-Cys-$(X)_5$-Arg-Thr	(SEQ ID NO:10)
His-Cys-$(X)_5$-Arg-Ser-Gly	(SEQ ID NO:11)
His-Cys-$(X)_5$-Arg-Thr-Gly	(SEQ ID NO:12)
Val-His-Cys-$(X)_5$-Arg-Ser	(SEQ ID NO:13)
Val-His-Cys-$(X)_5$-Arg-Ser-Gly	(SEQ ID NO:14)
Val-His-Cys-$(X)_5$-Arg-Thr	(SEQ ID NO:15)
Val-His-Cys-$(X)_5$-Arg-Thr-Gly	(SEQ ID NO:16)
Ile-His-Cys-$(X)_5$-Arg-Ser	(SEQ ID NO:17)
Ile-His-Cys-$(X)_5$-Arg-Ser-Gly	(SEQ ID NO:18)
Ile-His-Cys-$(X)_5$-Arg-Thr	(SEQ ID NO:19)
Ile-His-Cys-$(X)_5$-Arg-Thr-Gly	(SEQ ID NO:20)

wherein X can be any amino acid residue, natural or unnatural. PTPs include PTP1B and PTPs comprising the sequences as listed in Figure 6, and those PTPs known in the art as well as naturally-occurring splice-variants or mutants thereof, provided that such PTPs comprise the sequence of SEQ ID NO:1. PTPs also include dual specificity phosphatases, also known as DSPs. A DSP is a dual specificity phosphatase enzyme that can dephosphorylate a phosphorylated Tyr residue as well as phosphorylated Ser or Thr residues of proteins. Exemplary DSPs are listed in Figure 7 herein. Figure 7 also provides a sequence alignment of catalytic domain regions of DSP polypeptides. The DSPs also comprise the signature catalytic cysteine motif set forth in SEQ ID NO:1.

Further included in the definition of a PTP are variant or mutant polypeptides having at least 70%, 80%, 85%, 90%, 95%, 98%, or 99% identity to a sequence in Figure 6 or Figure 7 or to a sequence of any other PTP known in the art, provided that such variant or mutant polypeptides comprise a sequence of amino acids selected from any of the sequences set forth in SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 106, 107, and 109. Such a PTP variant has a polyepeptide sequence at least 70%, 80%, 85%, 90%, 95%, 98%, or 99% identity to a sequence of a full-length PTP disclosed herein or known in the art.

The term "PTP-SN" means a PTP, such as a classical PTP and/or a DSP, or a variant thereof (also termed herein as a cyclic sulfenylamide, hence the abbreviated term "PTP-SN"), as described herein, wherein the sulfur atom of the catalytic cysteine is covalently bonded to the main-chain nitrogen atom of the adjacent C-terminal residue. The main-chain nitrogen of an amino acid, as is well understood in the art, is the nitrogen that contributes to the formation of the peptide bond that forms the backbone of a peptide or polypeptide. A peptide bond is formed by elimination of water from the carboxyl group of one amino acid and the α-amino group of the next or adjacent amino acid, which is the amino acid that is situated toward the carboxy terminus of the polypeptide, that is, the adjacent C-terminal residue. A PTP that may form a PTP-SN can be any one of those known in the art as well as a naturally-occurring splice-variant or mutant that has a sequence selected from any of the sequences set forth in SEQ ID NOS:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21; or a sequence disclosed in Andersen et al. (2001 *Mol. Cell. Biol.* 21:7117; 2004 *FASEB J.* 18:8). The PTP-SN may also be formed from a PTP polypeptide variant that has at least 70%, 80%, 85%, 90%, 95%, 98%, or 99% sequence identity to a sequence shown or described in Figure 6 herein, Figure 7 herein, or disclosed in Andersen et al. (*supra,* 2001; 2004), provided such PTP-SN or PTP-SN polypeptide variant comprises a sequence set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 106, 107, and 109; wherein the sulfur atom of the catalytic cysteine is covalently bonded to the main-chain nitrogen atom of the adjacent C-terminal residue.

While all PTP-SN molecules comprise the signature catalytic cysteine motif sequence of SEQ ID NO:1, PTP-SNs may comprise any of the motif sequences selected from:

His-Cys-$(X)_5$-Arg	(SEQ ID NO:2)
Val-His-Cys-$(X)_5$-Arg	(SEQ ID NO:3)
Ile-His-Cys-$(X)_5$-Arg	(SEQ ID NO:4)
Cys-$(X)_5$-Arg-Ser	(SEQ ID NO:5)
Cys-$(X)_5$-Arg-Thr	(SEQ ID NO:6)
Cys-$(X)_5$-Arg-Ser-Gly	(SEQ ID NO:7)
Cys-$(X)_5$-Arg-Thr-Gly	(SEQ ID NO:8)
His-Cys-$(X)_5$-Arg-Ser	(SEQ ID NO:9)
His-Cys-$(X)_5$-Arg-Thr	(SEQ ID NO:10)
His-Cys-$(X)_5$-Arg-Ser-Gly	(SEQ ID NO:11)
His-Cys-$(X)_5$-Arg-Thr-Gly	(SEQ ID NO:12)
Val-His-Cys-$(X)_5$-Arg-Ser	(SEQ ID NO:13)
Val-His-Cys-$(X)_5$-Arg-Ser-Gly	(SEQ ID NO:14)
Val-His-Cys-$(X)_5$-Arg-Thr	(SEQ ID NO:15)
Val-His-Cys-$(X)_5$-Arg-Thr-Gly	(SEQ ID NO:16)
Ile-His-Cys-$(X)_5$-Arg-Ser	(SEQ ID NO:17)
Ile-His-Cys-$(X)_5$-Arg-Ser-Gly	(SEQ ID NO:18)
Ile-His-Cys-$(X)_5$-Arg-Thr	(SEQ ID NO:19)
Ile-His-Cys-$(X)_5$-Arg-Thr-Gly	(SEQ ID NO:20)
[I/V]HCXAGXXR[S/T]G	(SEQ ID NO:106)
C$(X)_5$-R[S/T]	(SEQ ID NO:107)
and CS-$(X)_4$-R	(SEQ ID NO:109);

wherein X is any amino acid residue, natural or unnatural, wherein the sulfur atom of the catalytic cysteine is covalently bonded to the main-chain nitrogen atom of the adjacent C-terminal residue. The PTP polypeptide that is not in the SN form described herein but which was used to make the particular PTP-SN is denoted as the

corresponding PTP polypeptide or corresponding wildtype PTP polypeptide. In certain embodiments, the PTP in a sulfenyl-amide form (PTP-SN) is any one of the classical PTPs or the DSPs described herein or known in the art, or a variant thereof, that has been oxidized to the inactive PTP-SN form. In a particular embodiment, the PTP is selected from PTP1B (SEQ ID NO:24, 26, 30) and DEP-1 (SEQ ID NO:38, 40). In certain other embodiments, the PTP is a DSP such as, for example, cdc14a (SEQ ID NO:85, 87, 89), cdc14b (SEQ ID NO:91, 93), cdc25a (SEQ ID NO:67, 69), cdc25b (SEQ ID NO:77, 79), cdc25c (SEQ ID NO:81, 83), or DSP-3/JSP-1 (SEQ ID NO:97).

The term "PTP-SS" means a PTP (a classical PTP or a DSP or a variant) as described herein, wherein the sulfur atom of the catalytic cysteine is covalently bonded to form a disulfide bond with the sulfur atom of a conformationally proximal or nearby cysteine residue. A PTP-SS may comprise a PTP known in the art as well as naturally-occurring splice-variants or mutants having a sequence selected from the group consisting of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 and 21, and may have a sequence disclosed herein and/or disclosed in Andersen et al. (2001 *Mol. Cell. Biol.* 21:7117). The PTP that forms a PTP-SS may be a PTP polypeptide variant having at least 70%, 80%, 85%, 90%, 95%, 98%, or 99% sequence identity to a sequence shown or described in Figure 6 herein, Figure 7 herein, or disclosed in Andersen et al. (2001 *Mol. Cell. Biol.* 21:7117), provided such PTP or PTP polypeptide variant comprises any one of the sequences set forth in SEQ ID Nos: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 106, 107, or 109; wherein the sulfur atom of the catalytic cysteine is covalently bonded to form a disulfide bond with the sulfur atom of a conformationally proximal or nearby cysteine residue. While all PTP-SN molecules comprise the signature catalytic cysteine motif sequence of SEQ ID NO:1, PTP-SSs of the invention comprise any of the motif sequences selected from:

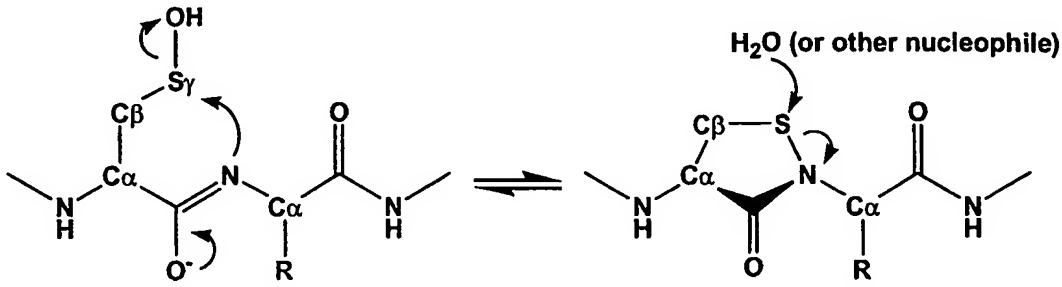
His-Cys-$(X)_5$-Arg	(SEQ ID NO:2)
Val-His-Cys-$(X)_5$-Arg	(SEQ ID NO:3)
Ile-His-Cys-$(X)_5$-Arg	(SEQ ID NO:4)
Cys-$(X)_5$-Arg-Ser	(SEQ ID NO:5)

Cys-$(X)_5$-Arg-Thr	(SEQ ID NO:6)
Cys-$(X)_5$-Arg-Ser-Gly	(SEQ ID NO:7)
Cys-$(X)_5$-Arg-Thr-Gly	(SEQ ID NO:8)
His-Cys-$(X)_5$-Arg-Ser	(SEQ ID NO:9)
His-Cys-$(X)_5$-Arg-Thr	(SEQ ID NO:10)
His-Cys-$(X)_5$-Arg-Ser-Gly	(SEQ ID NO:11)
His-Cys-$(X)_5$-Arg-Thr-Gly	(SEQ ID NO:12)
Val-His-Cys-$(X)_5$-Arg-Ser	(SEQ ID NO:13)
Val-His-Cys-$(X)_5$-Arg-Ser-Gly	(SEQ ID NO:14)
Val-His-Cys-$(X)_5$-Arg-Thr	(SEQ ID NO:15)
Val-His-Cys-$(X)_5$-Arg-Thr-Gly	(SEQ ID NO:16)
Ile-His-Cys-$(X)_5$-Arg-Ser	(SEQ ID NO:17)
Ile-His-Cys-$(X)_5$-Arg-Ser-Gly	(SEQ ID NO:18)
Ile-His-Cys-$(X)_5$-Arg-Thr	(SEQ ID NO:19)
Ile-His-Cys-$(X)_5$-Arg-Thr-Gly	(SEQ ID NO:20)
[I/V]HCXAGXXR[S/T]G	(SEQ ID NO:106)
$C(X)_5$-R[S/T]	(SEQ ID NO:107)
and CS-$(X)_4$-R	(SEQ ID NO:109);

wherein X is any amino acid residue, natural or unnatural, and wherein the sulfur atom of the catalytic cysteine is covalently bonded with the sulfur atom of a conformationally proximal or nearby cysteine residue to form a disulfide bond. The PTP polypeptide that is not in the SS form described herein but which was used to make the particular PTP-SS is denoted as the corresponding PTP polypeptide or corresponding wildtype PTP polypeptide that has been oxidized to form the sulfur-sulfur bond. In certain embodiments, the PTP in a cyclic sulfenyl-amide form (PTP-SN) is any one of any one of the classical PTPs or the DSPs described herein or known in the art, or a variant thereof. In a particular embodiment, the PTP is selected from PTP1B (SEQ ID NO:24, 26, 30) and DEP-1 (SEQ ID NO:38, 40). In certain other embodiments, the PTP is a DSP such as, for example, cdc14a (SEQ ID NO:85, 87, 89), cdc14b (SEQ ID NO:91,

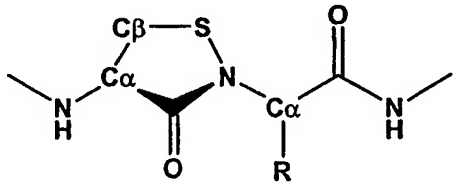
93), cdc25a (SEQ ID NO:67, 69), cdc25b (SEQ ID NO:77, 79), cdc25c (SEQ ID NO:81, 83), or DSP-3/JSP-1 (SEQ ID NO:97).

As used herein, the phrase "wherein the sulfur atom of the catalytic cysteine is covalently bonded to the main-chain nitrogen atom of the adjacent C-terminal residue" means the following structures (II) or (V)



sulfenic acid **cyclic sulfenamide**

(V)



(II)

wherein R is the side chain (or side group) of the C-terminal adjacent residue. The chemical composition and structure of the side chain of each amino acid are well known in the art (see also the linear structure presented in the table below).

Name	Linear Structure
Alanine (A)	CH3-CH(NH2)-COOH
Arginine (R)	HN=C(NH2)-NH-(CH2)3-CH(NH2)-COOH
Asparagine (N)	H2N-CO-CH2-CH(NH2)-COOH
Aspartic Acid (D)	HOOC-CH2-CH(NH2)-COOH
Cysteine (C)	HS-CH2-CH(NH2)-COOH
Glutamic Acid (E)	HOOC-(CH2)2-CH(NH2)-COOH
Glutamine (Q)	H2N-CO-(CH2)2-CH(NH2)-COOH
Glycine (G)	NH2-CH2-COOH
Histidine (H)	NH-CH=N-CH=C-CH2-CH(NH2)-COOH
Isoleucine (I)	CH3-CH2-CH(CH3)-CH(NH2)-COOH
Leucine (L)	(CH3)2-CH-CH2-CH(NH2)-COOH
Lysine (K)	H2N-(CH2)4-CH(NH2)-COOH
Methionine (M)	CH3-S-(CH2)2-CH(NH2)-COOH
Phenylalanine (F)	Ph-CH2-CH(NH2)-COOH
Proline (P)	NH-(CH2)3-CH-COOH
Serine (S)	HO-CH2-CH(NH2)-COOH
Threonine (T)	CH3-CH(OH)-CH(NH2)-COOH
Tryptophan (W)	Ph-NH-CH=C-CH2-CH(NH2)-COOH
Tyrosine (Y)	HO-Ph-CH2-CH(NH2)-COOH
Valine (V)	(CH3)2-CH-CH(NH2)-COOH

Portions of two PTP polypeptide sequences are regarded as having corresponding amino acid sequences, regions, fragments or the like, based on a convention of numbering one PTP sequence according to amino acid position number, and then aligning the sequence to be compared in a manner that maximizes the number of amino acids that match or that are conserved residues, for example, that remain polar (*e.g.*, D, E, K, R, H, S, T, N, Q), hydrophobic (*e.g.*, A, P, V, L, I, M, F, W, Y), or neutral (*e.g.*, C, G) residues at each position. A variety of criteria known to those skilled in the art indicate whether amino acids at a particular position in a peptide or polypeptide are similar. For example, a similar amino acid or a conservative amino acid substitution is

one in which an amino acid residue is replaced with an amino acid residue having a similar side chain, which include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine); acidic side chains (*e.g.*, aspartic acid, glutamic acid); uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, histidine); nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan); beta-branched side chains (*e.g.*, threonine, valine, isoleucine), and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan). Proline, which is considered more difficult to classify, shares properties with amino acids that have aliphatic side chains (*e.g.*, Leu, Val, Ile, and Ala). In certain circumstances, substitution of glutamine for glutamic acid or asparagine for aspartic acid may be considered a similar substitution in that glutamine and asparagine are amide derivatives of glutamic acid and aspartic acid, respectively.

Alignment may be achieved by comparing sequences, aligning the signature catalytic cysteine motif and other invariant or highly conserved amino acid residues, using computer algorithms well known to those having ordinary skill in the art, such as GENEWORKS, Align or the BLAST algorithm (Altschul, *J. Mol. Biol. 219*:555-565, 1991; Henikoff and Henikoff, *Proc. Natl. Acad. Sci. USA 89*:10915-10919, 1992), which is available at the NCBI website (see Internet>URL:http://www/ncbi.nlm.nih.gov/cgi-bin/BLAST>) (see also Andersen et al. (2001), *supra*; Andersen et al. (2004), *supra)*. Other sequence alignment algorithms, with which those having ordinary skill in the art will be familiar, may also be used.

A DNA sequence encoding a candidate PTP that is to be mutated as provided herein, or a portion, region, fragment or the like, may correspond to a known wildtype PTP-encoding DNA sequence according to a convention for numbering nucleic acid sequence positions in the known wildtype PTP-encoding DNA sequence, whereby the candidate PTP DNA sequence is aligned with the known PTP-encoding DNA such that at least 70%, and preferably at least 80%, 85%, at least 90%, at least 95%, or at least 98% of the nucleotides in a candidate PTP DNA-encoding sequence of at least 20 consecutive nucleotides are identical to a known PTP-encoding DNA sequence.

Modification of DNA may be performed by a variety of methods, including site-specific or site-directed mutagenesis of DNA encoding the PTP and the use of DNA amplification methods using primers to introduce and amplify alterations in the DNA template, such as PCR splicing by overlap extension (SOE). Site-directed mutagenesis is typically effected using a phage vector that has single- and double-stranded forms, such as M13 phage vectors, which are well-known and commercially available. Other suitable vectors that contain a single-stranded phage origin of replication may be used (*see, e.g.*, Veira et al., *Meth. Enzymol.* 15:3, 1987). In general, site-directed mutagenesis is performed by preparing a single-stranded vector that encodes the protein of interest (*e.g.*, a member of the PTP family). An oligonucleotide primer that contains the desired mutation within a region of homology to the DNA in the single-stranded vector is annealed to the vector followed by addition of a DNA polymerase, such as *E. coli* DNA polymerase I (Klenow fragment), which uses the double stranded region as a primer to produce a heteroduplex in which one strand encodes the altered sequence and the other the original sequence. Additional disclosure relating to site-directed mutagenesis may be found, for example, in Kunkel et al. (*Methods in Enzymol. 154*:367, 1987); and in U.S. Patent Nos. 4,518,584 and 4,737,462. The heteroduplex is introduced into appropriate bacterial cells, and clones that include the desired mutation are selected. The resulting altered DNA molecules may be expressed recombinantly in appropriate host cells to produce the modified protein.

The term "isolated" as used herein refers to removal of a molecule such as a PTP or PTP-SN from its natural source, environment or milieu (*e.g.*, removal of a protein from an intact cell source), and the term "purified" as used herein means that the PTP or PTP-SN is essentially free of association with other proteins or polypeptides, for example, as a purification product of recombinant host cell culture, or as a purified product from a non-recombinant source. An "isolated" polypeptide therefore is one that is removed from its original environment. Preferably, such polypeptides are at least about 90% pure, at least about 95% pure, or at least about 99% pure, for example, where such a degree of purity refers to the percentage of detectable PTP or PTP-SN that is present in a preparation

relative to other detectable polypeptides. The term "substantially purified" or "substantially isolated" as used herein means a mixture that contains a molecule such as a PTP or a PTP-SN that is essentially free of association with other proteins or polypeptides, but for the presence of known proteins that can be removed using conventional methods, such as by affinity chromatography with a specific antibody, and which substantially purified or substantially isolated PTP or PTP-SN retains its biochemical characteristics as described herein or retains its conformational properties.

The methods described herein may be used for identifying compounds or agents that bind to the oxidized cyclic sulfenyl-amide form of a PTP and prevent such PTP-SN from returning to its active cysteine thiol-containing state. Once identified, such agents or compounds should be useful for potentiating, stimulating, increasing the flux or signal through a pathway that is regulated by that PTP, and which in certain preferred embodiments is contemplated to be a pathway that is negatively regulated by the PTP. For example, a compound may be identified by crystallizing an isolated PTP-SN and then soaking (or incubating, immersing, exposing, bathing, contacting or otherwise administering) the crystal in a solution containing a candidate compound and determining if the compound binds to the PTP-SN according to X-ray crystallography methods described herein and known in the art (*see, e.g.,* Johnson and Blundell, *Protein Crystallography* (Academic Press 1976); Blundell et al. *Nat. Rev. Drug Discov.* 1:45-54 (2002)). Other methods for determining whether a compound binds to a PTP-SN include isothermal titration calorimetry in the solution state (Weber et al., *Curr. Opin. Struct. Biol.* 13:115-21 (2003); Ward et al., *Prog. Med. Chem.* 38:309-76 (2001); Cliff et al., *J. Mol. Recognit.* 16:383-91 (2003)) or surface plasmon resonance (*e.g.,* BIAcore, Biosensor, Piscataway, NJ).

OXIDATION/REDUCTION OF PTPs

Methods to make and test PTP-SN or PTP-SS forms are described herein. Because the inventors have discovered that the previously unknown, inactive cyclic-sulfenylamide form of a PTP is based on oxidation of amino acids within the –C-$(X)_5$-R-

motif (SEQ ID NO:1) (the PTP signature catalytic cysteine motif), a substantial number of known and distinct PTPs may also be oxidized into the inactive cyclic-sulfenylamide form (PTP-SN) or PTP-SS form. Thus, any PTP may be used to make a PTP-SN or PTP-SS form including, without limitation, the classical PTPs as described by Andersen et al. (2001) (*supra*) and Andersen et al., 2004 (*supra*) and DSPs, for example, phosphatases such as PTP-eta, PTP-epsilon, DEP-1 (CD148), SHP2, SHP1, cdc25a, cdc25b, cdc25c, cdc14a, cdc14b, DSP-2, DSP-3/JSP-1, DSP-4, DSP-5, DSP-6, DSP-7, DSP-8, DSP-9, DSP-10, DSP-11, DSP-12, DSP-13, DSP-14, DSP-15, DSP-16, DSP-17, DSP-18, CD45, etc. Such PTPs, whether in isolated or purified form or in whole cells, may be subjected to oxidizing conditions as described herein, including an oxidizing agent, for example, hydrogen peroxide, and/or with another agent that directly or indirectly promotes reactive oxygen species (ROS) generation, under conditions and for a time sufficient to permit the production of the PTP-SN or PTP-SS form.

Oxidation of a PTP to the PTP-SN form results in an oxidatively modified PTP that is incapable of its normal recognition or and/or binding to a PTP substrate, thus inhibiting its catalytic dephosphorylation activity. Oxidation conditions resulting in the PTP-SN form may be reversible and, thus, may be controlled such that when the catalytic cysteine in the inactive PTP-SN form is reduced, for instance by thiols, the PTP can be regenerated in an active enzymatic state. Exposure of the PTP-SN form to increasing concentrations of ROS, or to an oxidizing agent, may result, however, in irreversible oxidation to sulfinic ($-SO_2$) and sulfonic ($-SO_3$) acid forms of the PTP. As described in detail herein, analytical techniques such as protein crystallography and mass spectrometry analyses (such as matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry) may be used for determining whether a PTP is in the PTP-SN form or in an irreversibly oxidized form. Electron density maps may be calculated by Fourier transformations and may be visualized by using crystallography software programs with which those skilled in the art are familiar (*e.g.,* REFMAC (Collaborative Computational Project No. 4. The CCP4 suite: programs for protein crystallography, *Acta Crystallogr. D* 50:670-63 (1994)); XtalView, McRee, *J. Molecular Graphics* 10: 44-

46 (1992)). Determining oxidation conditions under which a PTP is reversibly oxidized or irreversibly oxidized may also be determined by additional methods described herein. These analyses include, for example, determining the oxidation conditions under which a substrate trapping mutant of the corresponding wildtype PTP is oxidized to the sulfenyl-amide state such that the substrate trapping mutant has a reduced capability (total loss or partial reduction) to bind to or to form a complex with its PTP substrate, and determining under what particular oxidation conditions the substrate trapping mutant PTP's decreased (or absent) substrate binding (or decreased or absent complex formation) may be reversible, and under what oxidation conditions such substrate binding may be irreversible.

As a representative example to illustrate the mechanism of the reversibility of redox regulation of a PTP, X-ray crystallography and mass spectrometry were integrated to monitor the structural changes of the PTP, PTP1B, that occur upon oxidation of its catalytic site cysteine. Efforts were undertaken to determine the structure of PTP1B with the catalytic cysteine in the physiologically relevant, reversibly oxidized, Cys-SOH state. Surprisingly, however, by incubating the PTP1B enzyme with stoichiometric amounts of H_2O_2, formation of sulfenic acid was not observed, but instead an unexpected modification of the catalytic site Cys residue was observed, a cyclic-sulfenyl-amide species as described herein (Fig 1A). Furthermore, the structure of PTP1B was determined at several stages during a time course of oxidation in response to H_2O_2. Unexpectedly, only conversion to the novel cyclic-sulfenyl-amide intermediate was detected, and not the Cys-SOH state (Fig. 1B). The electron density maps were consistent with a mixture being present of both reduced and cyclic-sulfenyl-amide conformational states. Importantly, there was no definitive evidence of a sulfenic acid structure, indicating according to non-limiting theory that the rate of formation of this intermediate may have been ratelimiting in the generation of the cyclic-sulfenyl-amide species. Alternative conformation refinement using REFMAC (Collaborative Computational Project No. 4. The CCP4 suite: programs for protein crystallography, *Acta Crystallogr. D* 50:670-63 (1994)) accounted for the observed electron density maps

and allowed the relative proportions of the reduced and sulfenyl-amide states to be estimated. The 75-minute time-point was consistent with an almost equal mixture of the reduced and sulfenyl-amide forms of PTP1B, whereas at 40 min, approximately 25% of the enzyme had converted to the sulfenyl-amide state. After a 16-hour incubation, most of the sulfenyl-amide species was oxidized to sulfonic acid, and this structure of PTP1B resembled PTP1B-SO_3 generated using pervanadate, a strong oxidizing agent. In these structures, the PTP and pTyr loops adopted the closed conformation, identical to reduced PTP1B.

The oxidation of the catalytic Cys to the cyclic-sulfenyl-amide state resulted in profound changes in the structure of the active site with inhibition of activity. PTP mediated catalysis occurs via a two-step mechanism involving a thiophosphate intermediate of the catalytic Cys. The active site of PTP1B is present as a pronounced cleft on the surface of the protein. Its base is formed by the PTP loop, which contains the catalytic Cys215 and residues of the PTP signature motif (residues 214-222) (Barford et al., *Annu. Rev. Biophys. Biomol. Struct.* 27:133-64 (1998); Denu et al., *Biochemistry* 37:5633-42 (1998)). The sides of the cleft are formed by three motifs: the pTyr loop, containing Tyr46, which defines the depth of the cleft (Jia et al., *Science* 268:1754-58 (1995)); the Q loop containing Gln262, which mediates hydrolysis of the cysteinyl phosphate catalytic intermediate (Pannifer et al., *J. Biol. Chem.* 273:10454-62 (1998)); and the WPD loop, which moves to close the active site following substrate binding and contains the essential Asp181 residue that functions in both stages of catalysis. In the catalytically active, reduced form of PTP1B, the PTP loop adopts a cradle conformation to bind the substrate phosphate and position the thiol group of the Cys for nucleophilic attack onto the substrate (Barford et al. (1998) *supra*; Jia et al. (1995), *supra*). The Sγ-atom of Cys215 accepts a hydrogen bond from the side chain of Ser222, and is within 3.6 Å of the main chain nitrogen atom of Ser216. In addition, the side chain of Tyr46 is directed towards the PTP loop and its phenolic hydroxyl group forms a hydrogen bond to the side chain of Ser216 of the PTP loop (Fig. 2A).

In the cyclic-sulfenyl-amide oxidized state of PTP1B (PTP1B-SN), a covalent bond formed between the Sγ-atom of Cys215 and the main chain nitrogen atom of Ser216 (Fig. 2B). Electron density maps in the region of the PTP loop indicated well-defined continuous density bridging the Sγ-atom of Cys215 and the main chain nitrogen atom of Ser216 (Fig. 1). Formation of this bond occurred via a nucleophilic attack of the main-chain nitrogen atom of Ser216 onto the electrophilic sulfur atom of the labile sulfenic acid, with concomitant release of water (Fig. 2D). Importantly, *Fo-Fc* electron density maps revealed that no additional oxygen atoms were attached to Sγ of Cys215 in the sulfenyl-amide species (Fig. 1). This observation was consistent, by way of non-limiting theory, with the occurrence of a nucleophilic substitution reaction (Fig. 2D). The resultant sulfenyl-amide covalent bond was a five-atom cyclic structure that has not been previously observed in proteins.

Conformational changes of the side chains of Cys215 and Ser216 accompanied generation of the sulfenyl-amide bond and triggered tertiary structural changes in both the PTP and pTyr loops (Fig. 2C). Residues Ser216 to Arg221 underwent a dramatic change of conformation that flipped the PTP loop out of the catalytic site. Notably, Gly218 shifted by approximately 7 Å, and the helical conformation of the PTP loop in reduced PTP1B (Gly218 is left-handed) converted to a reverse β-hairpin conformation, which imposed strain on the main-chain conformation of Arg221. The trigger for the conformational change of the PTP loop resulted from the loss of the Cys215 – Ser222 hydrogen bond and conformational constraints on the main chain of the PTP loop imposed by the sulfenyl-amide bond. The conformational shift of the Ser216 side chain in the cyclic-sulfenyl-amide structure disrupted the hydrogen bond to the hydroxyl group of Tyr46 and this promoted a displacement of Tyr46 to a solvent exposed position, accompanied by shifts of the entire pTyr recognition loop. Apart from the conformational changes of the PTP and pTyr loops, and side chain of Gln262 of the Q-loop, other regions of the structure remained unchanged on oxidation (Fig. 2C). The open conformation of the PTP loop in the sulfenyl-amide state exposed the Sγ-atom of Cys215, enhancing its accessibility for modification by thiols. Significantly, incubating

crystals of PTP1B-SN with either DTT or glutathione demonstrated quantitative reduction of the sulfenyl-amide cysteine, and a conformational change of both the PTP and pTyr loops to their catalytically active conformations. Interestingly, in PTP1B-SO_3, generated either using pervanadate, a strong oxidizing agent, or prolonged exposure to H_2O_2, the PTP and pTyr loops adopted the closed conformation.

In following the time-course of oxidation induced by H_2O_2 in the crystal of PTP1B, it was noted that the sulfenic acid (SOH) form of Cys 215 was rapidly converted to a cyclic-sulfenyl-amide species, facilitated according to non-limiting theory by the close proximity of the $S\gamma$ atom of Cys215 to the polarized amide nitrogen of Ser216 (Figs. 1 and 2) (*see* Barford et al., *Science* 263:1397-404 (1994)). To explore the oxidation of PTP1B in solution, the protein was subjected to varying amounts of H_2O_2 then, following trypsinisation, the mass of the active site Cys-containing peptide was examined by MALDI-TOF mass spectrometry (Fig. 3A). At high concentrations of H_2O_2, which caused irreversible oxidation of the active site Cys, a shift in M_r of +32 or +48 Da was readily detected, equivalent to the formation of the sulfinic (Cys-SO_2) or sulfonic acid (Cys-SO_3) derivatives, respectively. However, at the lower concentrations of H_2O_2, which induced reversible oxidation of PTP1B, formation of Cys215-SOH was not detected. Similar results were found for the intact protein. In the PTP1B C215S mutant, in which the active site Cys was replaced by Ser, there was no change in the mass of this peptide at any concentration of H_2O_2 (Fig. 3A). To test whether this failure to detect the sulfenic acid derivative was due to its rapid conversion to another species, such as sulfenyl-amide, pulse-chase analysis with $H_2{}^{18}O_2$ was performed. Incubation of PTP1B with a 1000-fold molar excess "heavy" $H_2{}^{18}O_2$ or "light" $H_2{}^{16}O_2$ (50 mM), which resulted in irreversible inactivation of the enzyme (Fig. 3B, left panel), led to production of sulfonic acid derivatives with a mass increase of +54 (all ^{18}O) or +48 (all ^{16}O) respectively (Fig. 3B, right panel). However, when PTP1B was pre-incubated with lower levels of $H_2{}^{18}O_2$, which led to reversible inhibition of PTP1B, and then chased with a >100-fold excess of $H_2{}^{16}O_2$, production of a sulfonic acid derivative of mass +50 (1, ^{18}O and 2, ^{16}O) was not detected, but only +48 (all ^{16}O) (Fig. 3B). This observation was

consistent with a mechanism, according to non-limiting theory, that at concentrations of peroxide that resulted in reversible inhibition of PTP1B, oxygen was rapidly eliminated from sulfenic acid, the first oxidized form of the active site Cys, to generate a more stable derivative, such as the sulfenyl-amide species (Fig. 2). Importantly, this species was formed in the presence of thiols.

Together, crystallographic and pulse-chase mass spectrometry data established a model for the inter-relationship of PTP1B oxidation states (Fig. 4A). Oxidation to the sulfenyl-amide state would be anticipated to inhibit the PTP's activity in a reversible manner, with the chemical and structural characteristics of the sulfenyl-amide species both suppressing irreversible oxidation to sulfinic and sulfonic acids and permitting modification of Cys215 by thiols to regenerate an active state of the enzyme. In order to examine the effects of the oxidation-mediated structural changes on the function of PTP1B, a substrate trapping mutant form of the PTP (Flint et al., *Proc. Natl. Acad. Sci USA* 94:1680-85 (1997)) was incubated together with the insulin receptor kinase (IRK), a physiological substrate of PTP1B (Elchelbly et al., *Science* 283:1544-48 (1999); Klaman et al., *Mol. Cell Biol.* 20:5479-89 (2000)), and ATP in the presence of increasing concentrations of H_2O_2. After incubation, complexes containing PTP1B were immunoprecipitated and blotted with antibodies to phosphotyrosine (Fig. 4B). At low concentrations of H_2O_2, which did not result in oxidation of PTP1B, a complex of the substrate trapping mutant and the IRK was recovered. However, at concentrations of H_2O_2 that resulted in oxidation, binding of PTP1B to the IRK was disrupted, consistent with inhibition of substrate recognition by oxidation. Interestingly, at these higher concentrations of H_2O_2, enhanced tyrosyl phosphorylation of PTP1B by the IRK was observed. Consistent with the oxidation-induced structural changes in PTP1B in which Tyr46 adopted a solvent exposed position, phosphorylation of a PTP1B mutant, in which Tyr46 was changed to Phe, was attenuated relative to the wild type enzyme (Fig. 4C). Such phosphorylation raises the possibility of an additional tier of control over the redox regulation of PTP1B.

It has been proposed that the catalytic cysteines of cdc25, the low molecular weight (Mr) PTP and the tumor suppressor phosphatase PTEN are protected from irreversible oxidation by disulfide bond formation with vicinal cysteines (*i.e.*, cysteine residues that occupy the same local or nearby space in a three-dimensional structure) (Fauman et al., *Cell* 93:617-25 (1998); Caselli et al., *J. Biol. Chem.* 273:32554-60 (1998); Lee et al., *J. Biol. Chem.* 277:20336-42 (2002)); however, the tyrosine-specific PTPs do not contain equivalent vicinal thiols at their active sites with the exception of the PTP-PEST subgroup, which does have vicinal cysteine residues as determined by amino acid sequence alignments with PTP1B and KAP (*see* Andersen et al., (2001) *supra* and Andersen et al., (2004), *supra*). The present disclosure, however, describes a novel alternative mechanism to prevent irreversible PTP oxidation, which may also facilitate formation of glutathionylated PTP derivatives (*e.g.*, PTP1B, Barrett et al., *Biochemistry* 38:6699-705 (1999)), thus allowing redox-dependent regulation of these enzymes (Fig. 4A). The inventors are the first to demonstrate a covalent modification of a main-chain peptide group and to demonstrate the potential reactivity of the amide nitrogen atom. The associated conformational changes of PTP1B as described herein illustrate how ROS function as second messengers by mediating cysteine oxidation coupled to an allosteric transition of protein structure. The invention embodies a novel oxidation-dependent post-translational modification, which may have implications for understanding mechanisms of redox signaling that are important in the regulation of gene expression and signal transduction (Herrlich et al., *Biochem. Pharmacol.* 59:35-41 (2000); Kim et al., *Cell* 109:383-96 (2002)).

In another embodiment, the crystalline coordinates of a PTP-SN (e.g., PTP1B-SN) may be used in structure-based screening for rational drug design (*see, e.g.*, Blundell et al., *Nat. Rev. Drug Discov.* 1:45-54 (2002); Carr et al., *Drug Discov. Today* 7: 522-27 (2002); Stewart et al., *Drug Discov. Today* 7:187-96 (2002); Rowland, R.S. *Curr. Opin. Drug Discov. Devel.* 5:613-19 (2002); *see also, e.g.*, Fejzo et al., *Curr. Top. Med. Chem.* 3:81-97 (2003); Hajduk et al., *J. Med. Chem.* 42:2315-17 (1999); van Dongen et al., *Drug Discov. Today* 7:471-78 (2002)). For example, coordinates may be used in

computer-aided drug design, using software and hardware readily available in the art. Further, the invention contemplates a recordable medium or computer-readable medium comprising the crystal coordinates of PTP1B-SN as shown in the Tables. Such recordable media and their uses as well as methods and materials for implementing rational drug design are well known in the art, for example, as disclosed in WO 200295035 A1; WO 2003006674 A1; and WO 2003006987 A1. For instance, computer-readable media include magnetic media and optically-readable media. Examples of magnetic media include a hard or fixed drive, a random access memory (RAM) chip, a floppy disk, digital linear tape (DLT), a disk cache, and a ZIP disk. Optically-readable media are exemplified by compact discs (*e.g.*, CD-read only memory (ROM), CD-rewritable (RW), and CD-R recordable), and digital versatile/video discs (DVD) (*e.g.*, DVD-ROM, DVD-RAM, and DVD+RW)).

In one embodiment, a method is provided for determining a three-dimensional structure for a target PTP1B-SN and also provided is a computer system or computer-readable media containing (a) atomic coordinate data listed in the specification, which defines the three-dimensional structure of PTP1B-SN, or at least its selected coordinates; (b) structure factor data derived from the atomic coordinate data cited above; (c) a Fourier transform of the atomic coordinate data cited above; (d) atomic coordinate data of a target PTP1B-SN generated by homology modeling of the target based on the data listed in the specification; (e) atomic coordinate data of a target PTP1B-SN generated by interpreting X-ray crystallographic data or NMR data by reference to any of the data listed in the specification; or (f) structure factor data derived from the atomic coordinate data of (c)-(e); and modeling the interaction between PTP1B-SN and an agent compound that modulates the PTP activity. In another embodiment, a method for rational drug design may be used for identifying an agent compound capable of altering the enzymatic activity of PTP1B, comprising (a) introducing information defining the conformation of a PTP1B-SN inhibitor complex molecule into a suitable computer program (the conformation identity defined by the coordinates given herein) that displays the three-dimensional structure of such PTP1B-SN; (b) creating a three-dimensional

structure of a test compound in the computer program; (c) displaying and superimposing the model of the test compound on the model of the PTP1B-SN; (d) assessing whether the test compound model fits spatially into a desired region of PTP1B-SN; (e) incorporating the test compound in a biological activity assay for PTP1B; and (f) determining whether the test compound alters or modulates enzymatic activity of PTP1B in the assay. Such rational drug design methods may also be used for any other PTP-SN or mutant PTP of interest described herein.

MUTANT PTPS THAT CONFORMATIONALLY RESEMBLE PTP-SN

In another embodiment, the present invention relates to the discovery that a mutant PTP with two mutations in the signature catalytic cysteine site motif has a three-dimensional structural conformation that is highly similar (or substantially similar) to the three-dimensional conformation of the herein described PTP-SN form of a corresponding PTP. For example, a PTP1B cysteine215-to-alanine (CA or C215A) and serine216-to-alanine (SA or S216A) double mutant results in a conformational change to the PTP1B polypeptide. Such double mutant may operate as a stable surrogate for the herein described PTP-SN molecule. Hence, assays useful for screening for agents or compounds or antibodies that bind to the double mutant would also likely identify agents, compounds, and/or antibodies that bind to the PTP-SN form. Related embodiments of the invention also contemplate antibodies or other binding proteins capable of specifically binding to such a double mutant PTP (*e.g.*, double mutant PTP1B) and their uses, for instance, as detection reagents in cells.

In one embodiment, the double mutant PTP comprises a substitution of the cysteine residue (which is the catalytic cysteine) in the signature catalytic cysteine site motif (-C-$(X)_5$-R-, SEQ ID NO:1) and a substitution of the residue that is the adjacent C-terminal residue to the cysteine residue. In a certain embodiment, the double mutant PTP comprises a substitution of the cysteine residue in the signature catalytic site motif (-C-$(X)_5$-R-, SEQ ID NO:1) and a substitution of a serine residue that is the adjacent C-terminal residue to the cysteine residue (-C-S-$(X)_4$-R-, SEQ ID NO:109). A double

mutant PTP may be derived from a classical PTP as described herein (see also Andersen et al. (2001), *supra*; Andersen et al. (2004), *supra*), the signature catalytic site motif of which is the amino acid sequence -H-C-S-X-G-X-G-R-X-G- (SEQ ID NO:21), wherein in the double mutant, the catalytic cysteine and the serine residue that is the adjacent C-terminal residue to the catalytic cysteine are replaced. The cysteine residue in the signature catalytic site motif may be replaced with an amino acid including alanine, aspartic acid, glutamic acid, valine, leucine, isoleucine, proline, phenylalanine, tryptophan, methionine, glycine, serine, threonine, tyrosine, asparagine, glutamine, lysine, arginine, or histidine or other natural or non-natural amino acids known in the art including derivatives, variants and the like. Non-natural amino acids may be derived from naturally occurring amino acids and may be substituted in a PTP polypeptide sequence according to methods known in the art (*see, e.g.,* Hosaka et al., *Curr. Opin. in Chem. Biol.* 6:809-15 (2002); Evrard et al., *Acta Cryst.* D55:430-35 (1999); Sisido et al., *Appl. Microbiol. Biotechnol.* 57:274-81 (2001)).

In a particular related embodiment, the catalytic cysteine residue of the PTP is replaced with an alanine residue. By way of example, a double mutant PTP1B (SEQ ID NO:110) that has a structural conformation similar to the structural conformation of the PTP1B-SN form comprises a substitution of the cysteine residue that is located at position 215 in the wildtype PTP1B amino acid sequence (SEQ ID NO:24, 26, 30) with an alanine residue and a substitution of the serine residue that is located at position 216 in the wildtype PTP1B amino acid sequence (SEQ ID NO:24, 26, 30) with an alanine residue. The PTP polypeptide that does not contain the mutations described herein but which was used to make the double mutant PTP is denoted as the corresponding PTP polypeptide or corresponding wildtype PTP polypeptide. In another embodiment, the PTP in a double mutant form is DEP-1.

The structural conformation of the double mutant PTP polypeptides, similar to the conformational changes observed in a PTP-SN, includes the tertiary structural changes in both the PTP and pTyr loops. The PTP loop flips out of the catalytic site, and the helical conformation of the PTP loop converts to a reverse β-hairpin

conformation, which imposes strain on the main-chain conformation of the arginine residue in the signature catalytic cysteine motif. The loss of the hydrogen bond between the catalytic cysteine, which has been replaced, and another residue (such as the residue that is the C-terminal residue adjacent to the arginine in the signature catalytic cysteine motif, which frequently is a serine or threonine residue (see Figures 6 and 7)) places conformational constraints on the main chain of the PTP loop. The substitution of the serine that is the adjacent C-terminal residue to the catalytic cysteine disrupts the hydrogen bond to the hydroxyl group of a tyrosine residue (for example, the Tyr46 residue in PTP1B), and this promotes a displacement of the tyrosine to a solvent exposed position, accompanied by shifts of the entire pTyr recognition loop. Apart from the conformational changes of the PTP and pTyr loops, and the side chain of a residue in the Q-loop (for example, Gln262 of the Q-loop in PTP1B), other regions of the structure remain unchanged.

Conformational changes of a double mutant PTP may be determined by X-ray crystallography, mass spectrometry, and computer molecular modeling and other techniques described herein and known in the art. Conformational changes may also be detected by using antibodies that specifically recognize a conformational epitope that is formed by a double mutant PTP but that is not present in the corresponding wildtype PTP. A conformational epitope or conformational antigenic determinant may be composed of amino acid residues from separated portions of the primary amino acid sequence that are spatially juxtaposed in the three-dimensional structure of a folded protein. A conformational epitope may also be composed of two or more adjacent amino acids in the primary amino acid sequence and other amino acids that are spatially juxtaposed in the three-dimensional structure to the adjacent amino acids.

Antibodies may be prepared according to methods described herein and known in the art that bind specifically to a double mutant PTP but do not bind to the corresponding wildtype PTP, and other antibodies may be prepared that bind to the wildtype PTP polypeptide but that do not specifically bind or recognize the double mutant PTP polypeptide. In a particular embodiment, the antibodies that specifically bind to a

double mutant PTP also specifically bind to the PTP in the cyclic sulfenyl amide form (PTP-SN) form. An antibody that specifically binds to the PTP-SN form may thus inhibit, hinder, protect, or prevent the PTP-SN from being reduced to the catalytically active form of the PTP. Such an antibody may be useful as a therapy for treating diseases or conditions associated with a signal transduction pathway in which the PTP is involved. For instance, without wishing to be bound by theory, an antibody or antigen binding fragment thereof that binds specifically to the PTP-SN form of PTP1B may trap the PTP1B in an inactive form and thus promote insulin signaling, which is useful for treating diabetes.

Immunodetection methods described herein and known to a skilled artisan may be routinely performed to identify such antibodies. For example, a conformational epitope may be identified by a monoclonal antibody that specifically binds to its cognate polypeptide antigen when the antigen is in its native state, but that fails to bind to the antigen when the conformation of the polypeptide antigen is disrupted, for instance when the antigen has been denatured.

PTP ASSAYS

As described herein, the presently disclosed sulfenyl amide (or cyclic-sulfenyl-amide) form of PTPs (PTP-SN), which result from oxidative PTP modification, lack PTP catalytic activity and also lack PTP substrate binding activity. As also noted herein, the oxidative PTP modification that gives rise to PTP-SN is reversible, such that subsequent reduction of the functionally inactive PTP-SN can yield an active PTP. Suitable assay conditions for determining PTP-mediated catalytic dephosphorylation of a PTP substrate tyrosine phosphorylated polypeptide can be readily determined without undue experimentation by a skilled person, based on the disclosure herein and known methods and properties of PTPs. Enzymatic activity assays are known in the art and may be modified according to the teachings herein; for example, assays of PTP activity using a tyrosine phosphorylated ^{32}P-labeled substrate are described in Flint et al. (1993 *EMBO J.* *12*:1937-1946). For instance, a substrate may be dephosphorylated *in vitro* by incubating

a PTP with a detectably labeled substrate peptide in a suitable buffer (*e.g.*, Tris, pH 7.5, 1 mM EDTA, 1 mM dithiothreitol, 1 mg/mL bovine serum albumin) for 10 minutes at 30°C. In general, and depending upon the particular assay type selected (*e.g.*, with regard to sensitivity and detection limits that may vary as a function of the reporter signal that is monitored, and further with regard to assay formats such as conventional test tubes or high throughput formats such as 96-well, 384-well or other high throughput microplates) the amounts of the reaction components may range from about 0.5-10 pg to about 50-500 ng of PTP polypeptide and from about 0.5 ng (0.1 ng for FP assays) to about 10 μg of substrate polypeptide. The extent of substrate dephosphorylation may generally be monitored by determining a fluorescence energy signal as described, for example, in WO 01/61031 using fluorescence polarization or FRET.

It is contemplated that the present invention will be of significant value in high throughput screening; *i.e.*, in automated screening of a large number of candidate compounds for activity against one or more PTPs. It has particular value, for example, in screening synthetic or natural product libraries for compounds that exhibit activity in affecting PTP binding and PTP catalysis in binding and catalytic assays as described herein. The methods described herein are therefore amenable to automated, cost-effective high throughput drug screening and have immediate application in a broad range of pharmaceutical drug development programs. In a preferred embodiment of the invention, the compounds to be screened are organized in a high throughput screening format such as a 96-well plate format, or other regular two dimensional array, such as a 384-well, 48-well or 24-well plate format or an array of test tubes. It is preferred, for example, that an automated apparatus for use according to high throughput screening embodiments is under the control of a computer or other programmable controller. The controller can continuously monitor the results of each step of the process and can automatically alter the testing paradigm in response to those results.

AGENTS

As noted above, the invention is directed in part to a method for identifying an agent that hinders or modulates the reduction of a PTP-SN or PTP-SS (throughout this section, the teachings apply to PTP-SS as well as PTP-SN), by combining a candidate agent such as a test compound with a PTP-SN to form a compound:PTP-SN composition, exposing the compound:PTP-SN composition to a reducing agent and also separately reducing the PTP-SN in the absence of the test compound, and evaluating the effect of the candidate agent on the phosphatase activity using, for example, a PTP activity assay described herein. An alteration in phosphatase activity (*e.g.*, statistically significant increase or decrease) can be determined and would, in the case of a compound that hinders or modulates PTP-SN reduction, preferably be expected to manifest as an increase in the detectable PTP catalytic activity of the separately reduced PTP-SN, relative to that detected in the compound:PTP-SN composition following exposure to the reducing agent. Without wishing to be bound by theory, according to such an assay, the test compound is believed to stabilize the PTP-SN (that is, stabilize the PTP-SN in the oxidized state) and thereby protect it from the reducing agent, which prevents conversion of the catalytically inactive PTP-SN to a catalytically active PTP. In general, a suitable amount of test compound (candidate agent) for use in such an assay ranges from about 0.001 μM to about 100 μM. The test compound (candidate agent) may be an endogenous physiological substance, an antibody, or may be a natural or synthetic drug, including small organic molecules.

Candidate agents for use as test compounds in screening assays according to the present invention may be provided as "libraries" or collections of compounds, compositions or molecules. Such molecules typically include compounds known in the art as "small molecules" and having molecular weights less than 10^5 daltons, preferably less than 10^4 daltons and still more preferably less than 10^3 daltons. For example, members of a library of test compounds can be administered to a plurality of samples in a high throughput screening array as provided herein, each containing at least one PTP-SN before and/or after exposure to reducing conditions sufficient to convert the PTP-SN to a

catalytically active PTP, and then assayed for the ability of the test compound (or candidate agent) to enhance or inhibit reduction of the PTP-SN. For example, identification of a compound that binds to a PTP-SN and that suppresses or decreases the rate at which the PTP-SN is reduced may be determined by a high throughput X-ray crystallography method. Stepwise, sequentially, or simultaneously and in any order, for example, after preparing a crystal of the isolated PTP-SN, a test compound and reducing agent may be added to the crystallized PTP-SN, and then the rate at which the rate the PTP-SN is reduced may be determined. A preferred compound is one that binds to the PTP-SN form and suppresses reversion of the PTP-SN to the native PTP state (*i.e.*, via reduction), thus inhibiting or blocking the capability of the PTP to bind and catalytically dephosphorylate a phosphorylated substrate. Compounds so identified as capable of influencing PTP-SN oxidation state (*e.g.*, stabilization) are valuable for therapeutic and/or diagnostic purposes since they permit treatment and/or detection of diseases associated with PTP activity. Such compounds are also valuable in research directed to molecular signaling mechanisms that involve PTPs, and to refinements in the discovery and development of future PTP-active compounds exhibiting greater specificity.

Candidate agents further may be provided as members of a combinatorial library, which preferably includes synthetic agents prepared according to a plurality of predetermined chemical reactions performed in a plurality of reaction vessels. For example, various starting compounds may be prepared employing one or more of solid-phase synthesis, recorded random mix methodologies and recorded reaction split techniques that permit a given constituent to traceably undergo a plurality of permutations and/or combinations of reaction conditions. The resulting products comprise a library that can be screened followed by iterative selection and synthesis procedures, such as a synthetic combinatorial library of peptides (*see e.g.*, PCT/US91/08694, PCT/US91/04666, which are hereby incorporated by reference in their entireties) or other compositions that may include small molecules as provided herein (see *e.g.*, PCT/US94/08542, EP 0774464, U.S. 5,798,035, U.S. 5,789,172, U.S. 5,751,629, which are hereby incorporated by reference in their entireties). Those having ordinary skill in

the art will appreciate that a diverse assortment of such libraries may be prepared according to established procedures, and tested using PTPs and appropriate PTP substrates, according to the present disclosure.

Agents identified according to the methods described herein would be useful in altering or modulating the reduction of the PTP-SN in vivo; and would be useful in treating a patient having a PTP-mediated condition or disease. Formulations of such agents into pharmaceutical compositions are well-known in the art and described herein.

ASSAYS UTILIZING PTP-SN, PTP-SS, OR DOUBLE MUTANT PTP

Compounds or agents that bind to the oxidized cyclic sulfenyl-amide form of a PTP and prevent it from returning to its active cysteine thiol containing state should be useful agents for potentiating, stimulating, increasing the flux or signal through a pathway that is negatively regulated by that PTP. For example, PTP1B is one such negative regulator of the insulin and leptin signaling pathways, and thus such compounds would be predicted to improve insulin or leptin sensitivity in diabetic or obese patients. To identify such agents, a variety of assay methodologies using the PTP-SN, PTP-SS, or double mutant PTP molecules of the invention could be applied. Such methods fall into two general classes: (a) assays that measures the ability of a candidate agent to slow, hinder, impair, suppress or otherwise decrease (*e.g.*, in a statistically significant manner) the restoration of enzyme activity to an oxidatively modified PTP (*e.g.*, PTP-SN or (PTP-SS) by a reducing agent, and (2) assays that measure binding of a candidate agent to the PTP-SN (or PTP-SS or mutant PTPs described herein) but without assessing the consequences of such binding on reappearance of enzyme activity. Any of the PTP polypeptides described herein and known in the art may be used in the methods and assays described herein. Such PTPs include but are not limited to PTP1B (SEQ ID NO:24, 26, 30), cdc14a (SEQ ID NO:85, 87, 89), cdc14b (SEQ ID NO:91, 93), cdc25a (SEQ ID NO:67, 69), cdc25b (SEQ ID NO:77, 79), cdc25c (SEQ ID NO:81, 83), DSP-3/JSP-1 (SEQ ID NO:97), and DEP-1 (SEQ ID NO:38, 40).

In one embodiment, the desired PTP-SN or PTP-SS, as described herein, may be produced or obtained in a substantially purified or substantially isolated form, or in an isolated or purified form, by using methods described herein or other means known in the art that provide controlled oxidation of the catalytic cysteine. Throughout this section, the term "PTP-SN" is used to illustrate certain assays of the invention, but it is understood that PTP-SN, for such purposes, may refer interchangeably to any of PTP-SN, PTP-SS, or the mutant PTPs described herein (with the exception being that restoration of catalytic activity by treatment with a reducing agent would not be expected using the mutant PTP). A representative assay comprises the following steps: (a) contacting (combining, mixing, adding together, or otherwise introducing a PTP-SN to a test compound to form a composition) the PTP-SN with a candidate agent, for example, a test compound that is a small organic molecule, (b) adding a reducing agent to the agent:PTP-SN composition (the composition being a mixture of the agent and PTP-SN in which a portion of or all of the agent present in the mixture may form a complex with a portion or all of the PTP-SN); non-limiting examples of reducing agents include the thiol-containing compounds such as beta-mercaptoethanol, dithiothreitol (DTT), dithioerythritol (DTE) or glutathione, or non-thiol reducing agents such as phosphines (*e.g.*, tris(2-carboxyethyl) phosphine (TCEP))); (c) measuring PTP activity (*e.g.*, catalytic dephosphorylation activity), for example either continuously or at a fixed time point after addition of the reducing agent; and (d) comparing the rate of appearance of PTP activity in the presence of the candidate agent to that measured in the absence of the candidate agent. By using such methods of the invention, it is now possible to determine whether such candidate agents are binding to the oxidized PTP (PTP-SN) and slowing, hindering, impairing, inhibiting, or preventing the reappearance of PTP activity (thereby providing means for modulating or altering PTP activity).

Alternatively, a representative assay comprises the following steps: (a) contacting a biological sample comprising a cell containing the desired PTP with a reactive oxygen species or other means for causing the PTP to be oxidized into the PTP-SN state; (b) contacting (combining, mixing, adding together or otherwise introducing a

PTP-SN to a test compound to form a composition) the PTP-SN containing cell with a candidate agent, for example, a test compound that is a small organic molecule, (c) adding a reducing agent to the agent:PTP-SN composition (the composition being a mixture of the agent and PTP-SN in which a portion of or all of the agent present in the mixture may form a complex with a portion or all of the PTP-SN); non-limiting examples of reducing agents include the thiol-containing compounds such as beta-mercaptoethanol, dithiothreitol (DTT), dithioerythritol (DTE) or glutathione, or non-thiol reducing agents such as phosphines (*e.g.*, tris(2-carboxyethyl) phosphine (TCEP))); (d) measuring PTP activity (*e.g.*, dephosphorylation catalytic activity), for example either continuously or at a fixed time point after addition of the reducing agent; and (e) comparing the rate of appearance of PTP activity in the presence of the candidate agent to that measured in the absence of the candidate agent. By using such methods of the invention, it is now possible to determine whether such candidate agents are binding to the oxidized PTP (PTP-SN) and slowing, hindering, inhibiting, or preventing the reappearance of PTP activity (thereby providing means for modulating or altering PTP activity).

A "biological sample" as used herein refers to a sample containing at least one protein tyrosine phosphatase, and may be provided by obtaining a blood sample, biopsy specimen, tissue explant, organ culture, or any other tissue or cell preparation from a subject or a biological source. A sample may further refer to a tissue or cell preparation in which the morphological integrity or physical state has been disrupted, for example, by dissection, dissociation, solubilization, fractionation, homogenization, biochemical or chemical extraction, pulverization, lyophilization, sonication or any other means for processing a sample derived from a subject or biological source.

The subject or biological source may be a human or non-human animal, a primary cell culture, or culture adapted cell line including but not limited to genetically engineered cell lines that may contain chromosomally integrated or episomal recombinant nucleic acid sequences, immortalized or immortalizable cell lines, somatic cell hybrid cell lines, differentiated or differentiatable cell lines, transformed cell lines and the like. Optionally, in certain situations it may be desirable to treat cells in a biological sample

with hydrogen peroxide and/or with another agent that directly or indirectly promotes reactive oxygen species (ROS) generation, including biological stimuli as described herein. In certain other situations it may be desirable to treat cells in a biological sample with a ROS scavenger, such as N-acetyl cysteine (NAC) or superoxide dismutase (SOD) or other ROS scavengers known in the art. In other situations cellular glutathione (GSH) may be depleted by treating cells with L-buthionine-SR-sulfoximine (Bso), and in other circumstances cells may be treated with pervanadate to enrich the sample in tyrosine phosphorylated proteins. Other means may also be employed to effect an increase in the population of tyrosine phosphorylated proteins present in the sample, including the use of a subject or biological source that is a cell line that has been transfected with at least one gene encoding a protein tyrosine kinase.

Various means are available to those skilled in the art for measuring the regeneration of an active PTP following reduction of the PTP-SN form. By way of non-limiting example, it is conventionally possible to measure the restored accessibility of the catalytic site thiol by reaction with a thiol-specific agent. Such thiol-specific agents are well known in the art and include Iac, IAM, and 4-vinyl pyridine. Detection can be determined by use of a detectable label, such as radioactive label, fluorescent label, biotin label, or Deuterium followed by detection using a mass spectrometer.

In another embodiment, the assays and methods described herein may be used for determining whether an agent specifically binds to a double mutant protein tyrosine phosphatase (PTP) polypeptide, that is, the agent does not bind to the corresponding wildtype PTP. The method may comprise contacting a double mutant PTP as described herein with a candidate agent or test compound under conditions and for a time sufficient to permit interaction between the mutant PTP and the candidate agent, and also contacting the corresponding wildtype PTP polypeptide with the candidate agent under conditions and for a time sufficient to permit interaction between the wildtype PTP and the candidate agent. The level of binding of the candidate agent to the mutant PTP may then be determined according to methods described herein and compared with the level of binding of the candidate agent to the wildtype PTP. An increased level of

binding of the agent or compound to the mutant PTP relative to the level of binding to the wildtype PTP indicates that the agent specifically binds to the mutant PTP polypeptide. Similarly, an agent that alters reduction of a PTP-SN may be identified by contacting, combining, or mixing, a candidate agent (or test compound) with a double mutant PTP and also combining the agent or compound with the corresponding wildtype PTP and comparing the level of binding of the agent or compound to each of the double mutant PTP and wildtype PTP. An increased or decreased level of binding of the agent to the mutant PTP indicates that the agent alters reduction of the corresponding PTP-SN.

An alternative representative assay comprises the steps of: (a) contacting a biological sample comprising a cell, such cell being capable of expressing the PTP, with a reactive oxygen species or other means for oxidizing the catalytic cysteine of the PTP to create a PTP-SN form; (b) contacting (combining, mixing, adding together, or otherwise introducing a biological sample to a test compound to form a composition) the biological sample or cell with a candidate agent such as, for example, a test compound that is a small organic molecule; (c) and measuring the binding of agent to protein. Step (c) can be accomplished by any of many described and conventional methods, including but not limited to thermal shift measurements, a technique that compares the thermal melting temperature shift of a free, unbound molecule compared to that of a molecule bound by an agent.

In a related embodiment, the assay may comprise a functional readout (*e.g.*, assessment of phosphoprotein phosphorylation state) to monitor whether the agent that binds to the PTP-SN also prevents restoration of PTP catalytic activity, for example, by observing persistent phosphorylation (*e.g.*, of a tyrosine residue) in a phosphorylated substrate using standard techniques. In another related embodiment, the assay may comprise a binding readout (*e.g.*, assessment of substrate binding by a substrate trapping mutant PTP) to monitor whether the agent that binds to the PTP-SN form of a substrate trapping mutant PTP also prevents restoration of substrate binding capability following exposure to a reducing agent, for example, using means for determining binding of a

suitable PTP substrate to the substrate trapping mutant PTP, such as those described herein and known to the art.

In another representative binding assay, a PTP-SN is produced or made in a substantially purified or substantially isolated form, or preferably in an isolated or purified form, using methods described herein or through other means that comprise controlled oxidation of the catalytic cysteine. The assay comprises the steps of (a) contacting the PTP-SN with a candidate agent such as, for example, a small organic molecule; (b) and measuring the binding of agent to protein.

Step (b) can be accomplished by any of many described and conventional methods, including but not limited to thermal shift measurements, a technique that compares the thermal melting temperature shift of a free unbound molecule compared to that of a molecule bound by an agent. Companies that have developed such thermal-shift technologies include Anadys Pharmaceuticals, San Diego, Calif., and 3D Pharmaceuticals (a Johnson and Johnson subsidiary) (*See also, e.g.*, Pantoliano et al., *J. Biomol. Screen.* 6:429-40 (2001)). Other variations for step (b) include measurement of mass changes, such as by detection using a mass spectrometer. Still other methods for measuring binding of agent to protein comprised in step (b) above include site-directed ligand discovery as discussed in the art by Erlanson, et al. (2000) *Proc. Natl. Acad. Sci. USA* 97:9367-937, and Arkin et al., *Proc. Natl. Acad. Sci. USA* 100: 1603-1608, each of which is incorporated herein by reference. In other embodiments, binding of a candidate compound to a PTP-SN, and/or to a double mutant PTP that conformationally mimics a PTP-SN as described herein, may be determined according to the methods described herein using nuclear magnetic resonance (NMR) (Fejzo et al., *supra*; Hajduk et al., *supra*; van Dongen et al., *supra*) or crystallography methods adapted for high throughput screening (Blundell et al., (2002), *supra*; Carr et al., *supra*; Stewart et al., *supra*; Rowland, *supra*).

In another embodiment, a method for identifying a compound that binds to a PTP-SN comprises contacting a PTP-SN with a test compound and determining binding of the compound to the PTP-SN by using an X-ray crystallography method. An isolated PTP-

SN may be crystallized according to methods described herein and known in the art. The step of contact a PTP-SN with a test compound when using an X-ray crystallography technique is understood to mean that the compound is soaked or incubated with the crystal in a solution containing the candidate compound. Binding of the compound to the PTP-SN may then be determined according to X-ray crystallography methods described herein and known in the art, for instance, by electron density mapping (*see, e.g.,* Johnson and Blundell, *Protein Crystallography* (Academic Press 1976); Blundell et al. *Nat. Rev. Drug Discov.* 1:45-54 (2002)).

In other embodiments, a method for determining whether a compound binds to a PTP-SN may include isothermal titration calorimetry in the solution state (Weber et al., *Curr. Opin. Struct. Biol.* 13:115-21 (2003); Ward et al., *Prog. Med. Chem.* 38:309-76 (2001); Cliff et al., *J. Mol. Recognit.* 16:383-91 (2003)); surface plasmon resonance (*e.g.,* BIAcore, Biosensor, Piscataway, NJ); or capilalary electrophoresis (*see, e.g.,* Cetek, Inc.).

ANTIBODIES

Also contemplated by the present invention are binding molecules that are peptides, polypeptides, and other non-peptide molecules that specifically bind to a PTP-SN and that specifically bind to a double mutant of the corresponding PTP as described herein. Such binding molecules can be used in a process for purifying the PTP-SN or the double mutant PTP, used for a therapy for treating a disease or condition associated with the PTP, or used in a diagnostic assay. As used herein, a molecule is said to specifically bind to a particular PTP-SN or to the particular double mutant PTP if it reacts at a detectable level with the PTP-SN and the double mutant PTP but does not react detectably with peptides containing an unrelated sequence or with a different phosphatase. Preferred binding molecules include antibodies, which may be, for example, polyclonal, monoclonal, single chain, chimeric, humanized, anti-idiotypic, or CDR-grafted immunoglobulins, or antigen-binding fragments thereof, such as proteolytically generated or recombinantly produced immunoglobulin $F(ab')_2$, Fab, Fab', Fv, and Fd fragments. An antibody according to the present invention may belong to any

immunoglobulin class, for example IgG, IgE, IgM, IgD, or IgA. It may be obtained from or derived from an animal, for example, fowl (*e.g.*, chicken) or a mammal, which includes but is not limited to a mouse, rat, hamster, rabbit, or other rodent, a cow, horse, sheep, goat, camel, human, or other primate. The antibody may be an internalising antibody, or the antibody may be modified so that it may be easily transported across a cell membrane.

Certain preferred antibodies are those antibodies that inhibit, hinder, or block PTP-SN from being reactivated to a catalytically active PTP; such antibodies also specifically bind to a double mutant of the corresponding PTP as described herein. Binding properties of an antibody to PTP-SN and to the double mutant of the corresponding PTP may generally be assessed using conventional immunodetection methods including, for example, an enzyme-linked immunosorbent assay (ELISA), immunoprecipitation, radioimmunoassays, immunoblotting and the like, which may be readily performed by those having ordinary skill in the art. A skilled artisan will also be familiar with such immunodetection methods that when used to detect an antibody that binds to a conformational epitope of a polypeptide, the method may require that any reagent or condition which could potentially denature the polypeptide and thus alter or destroy the conformational epitope be avoided or minimized.

In one embodiment, the antibody or antigen binding fragment thereof binds to an epitope that includes the catalytic cysteine residue in the sulphenyl-amide form. The epitope may comprise amino acid residues that are present in a contiguous segment of the sequence and that includes the catalytic cysteine. In another embodiment, the antibody or antigen binding fragment thereof binds to a conformational epitope that is formed in a sulphenyl-amide species of the PTP. In another embodiment, the antibody or antigen-binding fragment thereof binds to a double mutant PTP that has a substitution of the catalytic cysteine residue and a substitution of the adjacent C-terminal residue (*e.g.*, in a classical PTP, a substitution of cysteine with alanine and a substitution of the serine residue with an alanine residue). Such an antibody would also specifically bind to the PTP in the PTP-SN form. In a particular embodiment, the antibody or antigen binding fragment thereof recognizes a conformational epitope that results from conformational

changes that occur in the double mutant PTP as a result of the amino acid substitutions, and which conformational epitope is not present in the corresponding wildtype PTP.

Methods well known in the art and described herein may be used to generate antibodies, including polyclonal antisera or monoclonal antibodies, that are specific for a PTP-SN or a double mutant PTP. Antibodies also may be produced as genetically engineered immunoglobulins (Ig) or Ig fragments designed to have desirable properties. For example, by way of illustration and not limitation, antibodies may include a recombinant IgG that is a chimeric fusion protein having at least one variable (V) region domain from a first mammalian species and at least one constant region domain from a second, distinct mammalian species (*see, e.g.,* Morrison et al., *Proc. Natl. Acad. Sci. USA*, 81:6851-55 (1984); Shin et al., *Methods Enzymol.* 178:459-76 (1989); Walls et al., *Nucleic Acids Res.* 21:2921-29 (1993); U.S. Patent No. 5,482,856). Most commonly, a chimeric antibody has murine variable region sequences and human constant region sequences. Such a murine/human chimeric immunoglobulin may be "humanized" by grafting the complementarity determining regions (CDRs) derived from a murine antibody, which confer binding specificity for an antigen, into human-derived V region framework regions and human-derived constant regions (*see, e.g.*, Jones et al., *Nature* 321:522-25 (1986); Riechmann et al., *Nature* 332:323-27 (1988); Padlan et al., *FASEB* 9:133-39 (1995); Chothia et al., *Nature*, 342:377-383 (1989); Bajorath et al., *Ther. Immunol.* 2:95-103 (1995); EP-0578515-A3). Fragments of these molecules may be generated by proteolytic digestion, or optionally, by proteolytic digestion followed by mild reduction of disulfide bonds and alkylation. Alternatively, such fragments may also be generated by recombinant genetic engineering techniques.

An antibody that is immunospecific or that specifically binds to a PTP-SN polypeptide, PTP-SS, and/or a double mutant PTP as provided herein reacts at a detectable level with PTP-SN, PTP-SS, and/or a double mutant PTP and not with unrelated polypeptides, preferably with an affinity constant, K_a, of greater than or equal to about 10^4 M^{-1}, more preferably of greater than or equal to about 10^5 M^{-1}, more preferably of greater than or equal to about 10^6 M^{-1}, and still more preferably of greater

than or equal to about 10^7 M^{-1}. Affinity of an antibody for its cognate antigen is also commonly expressed as a dissociation constant K_D, and an anti-PTP (or PTP-SN, PTP-SS, or double mutant PTP) antibody specifically binds to the PTP if it binds with a K_D of less than or equal to 10^{-4} M, less than or equal to about 10^{-5} M, less than or equal to about 10^{-6} M, less than or equal to 10^{-7} M, or less than or equal to 10^{-8} M. Affinities of binding partners or antibodies can be readily determined using conventional techniques, for example, those described by Scatchard et al. (*Ann. N.Y. Acad. Sci. USA* 51:660 (1949)) or by surface plasmon resonance (BIAcore, Biosensor, Piscataway, NJ). *See, e.g.,* Wolff et al., *Cancer Res.* 53:2560-2565 (1993).

Antibodies may generally be prepared by any of a variety of techniques known to those skilled in the art. *See, e.g.,* Harlow et al., *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory (1988). In one such technique, an animal is immunized with the immunogen PTP-SN or a double mutant PTP, or a fragment or peptide thereof, as an antigen to generate polyclonal antisera. Suitable animals include, for example, rabbits, sheep, goats, pigs, cattle, and may also include smaller mammalian species, such as mice, rats, and hamsters, or other species.

An immunogen may be comprised of cells expressing PTP-SN, PTP-SS, or double mutant PTP, purified or partially purified PTP-SN, PTP-SS, or double mutant PTP, polypeptides, or variants or fragments (*e.g.*, a fragment comprising the PTP catalytic domain or a portion thereof) thereof, or PTP-SN peptides. PTP-SN peptides may be generated by proteolytic cleavage or may be chemically synthesized. Similarly, immunogens that may be used to generate antibodies that specifically bind to the double mutant PTP may be comprised of cells expressing the double mutant PTP, purified or partially purified double mutant PTP polypeptides, or variants or fragments (*e.g.*, a fragment comprising the catalytic domain) or peptides thereof. Fragments and/or peptides may be generated by proteolytic cleavage or may be chemically synthesized. For instance, nucleic acid sequences encoding PTP-SN polypeptides and double mutant PTPs polypeptides are provided herein, such that those skilled in the art may routinely prepare these polypeptides for use as immunogens. Peptides may be chemically synthesized by

methods as described herein and known in the art. Alternatively, peptides may be generated by proteolytic cleavage of a PTP-SN polypeptide, and individual peptides isolated by methods known in the art such as polyacrylamide gel electrophoresis or any number of liquid chromatography or other separation methods.

Peptides useful as immunogens typically may have an amino acid sequence of at least 4 or 5 consecutive amino acids from a PTP-SN or PTP-SS amino acid sequence or a double mutant PTP amino acid sequence such as those described herein, and preferably have at least 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 18, 19 or 20 consecutive amino acids of a PTP-SN or PTP-SS polypeptide or a double mutant PTP polypeptide. Certain other preferred peptide immunogens may comprise 21-25, 26-30, 31-35, 36-40, 41-50 or more consecutive amino acids of a PTP-SN or PTP-SS polypeptide sequence or a double mutant PTP polypeptide sequence. Polypeptides or peptides useful for immunization may also be selected by analyzing the primary, secondary, and tertiary structure of PTP-SN or a double mutant PTP polypeptide according to methods known to those skilled in the art, in order to determine amino acid sequences more likely to generate an antigenic response in a host animal. *See, e.g.*, Novotny, 1991 *Mol. Immunol. 28*:201-207; Berzofsky, 1985 *Science* 229:932-40; Chang et al. *J. Biochem.* 117:863-68 (1995); Kolaskar et al. *Viology* 261:31-42 (1999)). Such polypeptide fragment or peptide may comprise the signature catalytic cysteine motif (SEQ ID NO:1) or any of SEQ ID NOS:2-21, 106, 107, and 109. Preferably, the polypeptide or peptide comprises a sufficient number of amino acids to fold in a manner that approximates the conformation of the catalytic domain in a full-length PTP-SN or PTP-SS or double mutant PTP polypeptide.

Immunogens may be prepared and animals immunized according to methods well known in the art. *See, e.g.*, Harlow et al., *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory (1988). The immune response may be monitored by periodically bleeding the animal, separating the sera out of the collected blood, and analyzing the sera in an immunoassay, such as an ELISA or Ouchterlony diffusion assay, or the like, to determine the specific antibody titer. Once an antibody

titer is established, the animals may be bled periodically to accumulate the polyclonal antisera. Polyclonal antibodies that bind specifically to the PTP-SN or PTP-SS polypeptide or peptide (or to the double mutant PTP polypeptide or peptide) may then be purified from such antisera, for example, by affinity chromatography using protein A, an antibody that specifically binds to a constant region (heavy or light chain) of the antibody(ies) to be purified, or the PTP-SN polypeptide (or the double mutant PTP polypeptide), immobilized on a suitable solid support.

Monoclonal antibodies that specifically bind to PTP-SN or to PTP-SS polypeptides or fragments or variants thereof, (or to double mutant PTP polypeptides or fragments or variants thereof) and hybridomas, which are immortal eukaryotic cell lines, that produce monoclonal antibodies having the desired binding specificity, may also be prepared, for example, using the technique of Kohler and Milstein (*Nature, 256*:495-497; 1976, *Eur. J. Immunol. 6*:511-519 (1975)) and improvements thereto with which a skilled artisan is familiar. An animal—for example, a rat, hamster, or a mouse—is immunized with a PTP-SN or PTP-SN immunogen, lymphoid cells that include antibody-forming cells, typically spleen cells, are obtained from the immunized animal and may be immortalized by fusion with a drug-sensitized myeloma (*e.g.*, plasmacytoma) cell fusion partner.

Monoclonal antibodies may be isolated from the supernatants of hybridoma cultures or isolated from a mouse that has been treated (*e.g.*, pristane-primed) to promote formation of ascites fluid containing the monoclonal antibody. Antibodies may be purified by affinity chromatography using an appropriate ligand selected based on particular properties of the monoclonal antibody (*e.g.*, heavy or light chain isotype, binding specificity, etc.). Examples of a suitable ligand, immobilized on a solid support, include Protein A, Protein G, an anti-constant region (light chain or heavy chain) antibody, an anti-idiotype antibody and a PTP-SN or PTP-SN polypeptide or fragment or variant thereof (or to a double mutant PTP polypeptide or fragment or variant thereof).

Human monoclonal antibodies may be generated by any number of techniques with which those having ordinary skill in the art will be familiar. Antibodies

may also be identified and isolated from human immunoglobulin phage libraries, from rabbit immunoglobulin phage libraries, and/or from chicken immunoglobulin phage libraries (*see, e.g.,* Winter et al., 1994 *Annu. Rev. Immunol.* 12:433-55; Burton et al., 1994 *Adv. Immunol.* 57:191-280; U.S. Patent No. 5,223,409; Huse et al., 1989 *Science* 246:1275-81; Schlebusch et al., 1997 *Hybridoma* 16:47-52 and references cited therein; Rader et al., *J. Biol. Chem.* 275:13668-76 (2000); Popkov et al., *J. Mol. Biol.* 325:325-35 (2003); Andris-Widhopf et al., *J. Immunol. Methods* 242:159-31 (2000)). Antibodies isolated from non-human species or non-human immunoglobulin libraries may be genetically engineered according to methods described herein and known in the art to "humanize" the antibody or fragment thereof.

In certain embodiments, a B cell from an immunized animal that is producing an anti-PTP-SN, PTP-SN, or an anti-mutant PTP, including an anti-double mutant PTP, antibody is selected and the light chain and heavy chain variable regions are cloned from the B cell according to molecular biology techniques known in the art (WO 92/02551; US patent 5,627,052; Babcook et al., *Proc. Natl. Acad. Sci. USA* 93:7843-48 (1996)) and described herein. Preferably B cells from an immunized animal are isolated from the spleen, lymph node, or peripheral blood sample by selecting a cell that is producing an antibody that specifically binds to PTP-SN or to a double mutant PTP. B cells may also be isolated from humans, for example, from a peripheral blood sample.

An antibody fragment may also be any synthetic or genetically engineered protein that acts like an antibody in that it binds to a specific antigen to form a complex. For example, antibody fragments include isolated fragments consisting of the light chain variable region; "Fv" fragments consisting of the variable regions of the heavy and light chains; recombinant single chain polypeptide molecules in which light and heavy variable regions are connected by a peptide linker (scFv proteins); and minimal recognition units consisting of the amino acid residues that mimic the hypervariable region. Such an antibody fragment preferably comprises at least one variable region domain. (*see, e.g.*, Bird et al., *Science* 242:423-26 (1988); Huston et al., *Proc. Natl. Acad. Sci. USA* 85:5879-5883

(1988); EP-B1-0318554; U.S. Patent No. 5,132,405; U.S. Patent No. 5,091,513; and U.S. Patent No. 5,476,786).

In certain embodiments, an antibody that specifically binds to a PTP-SN or to a double mutant PTP may be an antibody that is expressed as an intracellular protein. Such intracellular antibodies are also referred to as intrabodies and may comprise an Fab fragment, or preferably comprise a scFv fragment (*see, e.g.*, Lecerf et al., *Proc. Natl. Acad. Sci. USA* 98:4764-49 (2001)). The framework regions flanking the CDR regions can be modified to improve expression levels and solubility of an intrabody in an intracellular reducing environment (*see, e.g.*, Worn et al., *J. Biol. Chem.* 275:2795-803 (2000)). An intrabody may be directed to a particular cellular location or organelle, for example by constructing a vector that comprises a polynucleotide sequence encoding the variable regions of an intrabody that may be operatively fused to a polynucleotide sequence that encodes a particular target antigen within the cell (*see, e.g.*, Graus-Porta et al., *Mol. Cell Biol.* 15:1182-91 (1995); Lener et al., *Eur. J. Biochem.* 267:1196-205 (2000)). An intrabody may be introduced into a cell by a variety of techniques available to the skilled artisan including via a gene therapy vector, or a lipid mixture (*e.g.*, Provectin™ manufactured by Imgenex Corporation, San Diego, CA), or according to photochemical internalization methods.

The polynucleotides encoding an antibody or fragment thereof that specifically bind a PTP-SN, PTP-SS, or double mutant PTP, as described herein, may be propagated and expressed according to any of a variety of well-known procedures for nucleic acid excision, ligation, transformation, and transfection using any number of known expression vectors. Thus, in certain embodiments expression of an antibody fragment may be preferred in a prokaryotic host, such as *Escherichia coli* (*see, e.g.*, Pluckthun et al., 1989 *Methods Enzymol.* 178:497-515). In certain other embodiments, expression of the antibody or a fragment thereof may be in a eukaryotic host cell, including yeast (*e.g.*, *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, and *Pichia pastoris*), animal cells (including mammalian cells) or plant cells. Examples of suitable

animal cells include, but are not limited to, myeloma, COS, CHO, or hybridoma cells. Examples of plant cells include tobacco, corn, soybean, and rice cells.

Antibodies that specifically bind to a PTP-SN and the corresponding double mutant PTP may be used in assays described herein for screening of candidate or test compounds that promote the cyclic sulfenyl-amide form of the PTP. In another embodiment, such antibodies that specifically bind to the PTP-SN may be used in screening assays to identify compounds that shift the active PTP:inactive PTP-SN equilibrium toward the inactive PTP-SN form.

In certain preferred embodiments, an antibody or antigen binding fragment thereof that specifically binds to a PTP-SN or PTP-SS may be delivered to the interior of a cell as an intact polypeptide. For example, methods to deliver exogenous proteins intracellularly may include the use of protein transduction domains as peptide carriers, for example, HIV-1 TAT, *Drosophila* Antennapedia homeotic transcription factor, and herpes simplex virus-1 DNA binding protein VP22 (Schwarze et al., *Trends Cell Biol.* 10:290-95 (2000). To intracellularly deliver an active protein, correct renaturation of the antibody or antigen-binding fragment thereof is required upon internalization of the protein by the cell. Such delivery systems may require that the antibody be covalently linked to the delivery molecule and/or chemical modification of the polypeptide. Another delivery system provides an amphipathic peptide carrier that can form a non-covalent complex with the antibody or antigen binding fragment thereof to be delivered to the cell (*see* Chariot™, Active Motif®, Carlsbad, CA; Morris et al., *J. Biol. Chem.* 274:24941-46 1999); Morris et al., *Nature Biotechnol.* 19:1173-76 (2110)). In another embodiment, the antibody or an antigen binding fragment thereof may be site-specifically attached to a peptide that comprises a membrane transport sequence that facilitates transport across membranes (*see, e.g.,* Zhao et al., J. Immunol. Methods 254:137-45 (2001); *see also, e.g.,* InNexus Biotechnology Inc. (Vancouver, BC, Canada)).

THERAPEUTIC METHODS

One or more antibodies or agents identified according to the above-described methods may also be used to modulate (*e.g.*, inhibit or potentiate) target polypeptide activity in a patient. As used herein, a "patient" may be any mammal, including a human, and may be afflicted with a condition associated with undesired target polypeptide activity or may be free of detectable disease. Accordingly, the treatment may be of an existing disease or may be prophylactic. Conditions associated with signal transduction and/or with inappropriate activity of specific PTP polypeptides described herein include obesity, impaired glucose tolerance and diabetes and cancer, disorders associated with cell proliferation, including cancer, graft-versus-host disease (GVHD), autoimmune diseases, allergy or other conditions in which immunosuppression may be involved, metabolic diseases, abnormal cell growth or proliferation, and cell cycle abnormalities.

For administration to a patient, one or more antibodies or agents are generally formulated as a pharmaceutical composition. A pharmaceutical composition may be a sterile aqueous or non-aqueous solution, suspension or emulsion, which additionally comprises a physiologically acceptable carrier (*i.e.*, a non-toxic material that does not interfere with the activity of the active ingredient). Such compositions may be in the form of a solid, liquid or gas (aerosol). Alternatively, compositions of the present invention may be formulated as a lyophilizate or compounds may be encapsulated within liposomes using well known technology. Pharmaceutical compositions within the scope of the present invention may also contain other components, which may be biologically active or inactive. Such components include, but are not limited to, buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, stabilizers, dyes, flavoring agents, and suspending agents and/or preservatives.

Any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of the present invention. Carriers for

therapeutic use are well known, and are described, for example, in *Remingtons Pharmaceutical Sciences*, Mack Publishing Co. (A.R. Gennaro ed. 1985). In general, the type of carrier is selected based on the mode of administration. For example, a pharmaceutical composition (*e.g.*, for oral administration or delivery by injection) may be in the form of a liquid (*e.g.*, an elixir, syrup, solution, emulsion or suspension). A liquid pharmaceutical composition may include, for example, one or more of the following: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or diglycerides which may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. A parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. The use of physiological saline is preferred, and an injectable pharmaceutical composition is preferably sterile.

The compositions described herein may be formulated for sustained release (*i.e.*, a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such compositions may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain an agent dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Within a pharmaceutical composition, a therapeutic agent may be linked to any of a variety of compounds. For example, such an agent may be linked to a targeting moiety (*e.g.*, a monoclonal or polyclonal antibody, a protein or a liposome) that facilitates the delivery of the agent to the target site. As used herein, a "targeting moiety" may be any substance (such as a compound or cell) that, when linked to an agent enhances the transport of the agent to a target cell or tissue, thereby increasing the local concentration of the agent. Targeting moieties include antibodies or fragments thereof, receptors, ligands, and other molecules that bind to cells of, or in the vicinity of, the target tissue. An antibody targeting agent may be an intact (whole) molecule, a fragment thereof, or a functional equivalent thereof. Linkage is generally covalent and may be achieved by, for example, direct condensation or other reactions, or by way of bi- or multi-functional linkers. Targeting moieties may be selected based on the cell(s) or tissue(s) toward which the agent is expected to exert a therapeutic benefit.

Pharmaceutical compositions may be administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dosage and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient and the method of administration. In general, an appropriate dosage and treatment regimen provides the agent(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.*, an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity). For prophylactic use, a dose should be sufficient to prevent, delay the onset of, or diminish the severity of a disease associated with cell proliferation.

Optimal doses may generally be determined using experimental models and/or clinical trials. In general, the amount of PTP-specific agent or antibody in a dose ranges from about 0.01 μg to about 100 μg per kg of host weight, typically from about 0.1 μg to about 10 μg. The minimum dose that is sufficient to provide effective therapy is usually preferred. Patients may generally be monitored for therapeutic or prophylactic

effectiveness using assays suitable for the condition being treated or prevented, which will be familiar to those having ordinary skill in the art. Suitable dose sizes will vary with the size, age, and/or mass of the patient, but will typically range from about 10 ml to about 500 ml for a 10-60 kg subject.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLE 1

OXIDATION AND REDUCTION OF PTP1B

Crystals of PTP1B oxidized in solution followed by crystallization. Purified PTP1B (Barford et al. (1994), *supra*) was dialyzed into DTT free buffer A (10 mM Tris pH 7.5, 25 mM NaCl, 0.2 mM EDTA). After dialysis, the protein concentration was 32 μM, and 40 μM H_2O_2 was added (ratio of 1:1.25). The protein was oxidized for 50 min at room temperature (RT) and concentrated to 8.5 mg/ml and crystallized (*id.*) without DTT. Data were collected on crystals at 3 weeks and 3 months after the protein was put into crystallization trials. The structures were solved as described for the time course of oxidation (see below).

Crystallization followed by oxidation. The catalytic domain of PTP1B (residues 1-321) was purified and crystallized at 4 °C (*id.*). To oxidize the protein, crystals were first washed for 1-2 minutes in 40 μl of crystallization well solution (0.1 M Hepes, pH 7.5, 0.2 M MgOAc, 0.2 mM EDTA, and PEG ranging from 12-17%) to remove the DTT. The crystals were then transferred to 40 μl of crystallization well solution plus 50 μM H_2O_2. They were soaked for time periods ranging from 20 min to 16 h (*see* Table 1) before being frozen in cryoprotectant buffer (0.1 M Hepes pH 7.5, 0.2 M MgOAc, 0.2 mM EDTA, 17.5% methyl-pentane diol, and PEG ranging from 18-20%). Data were collected at Chester Beatty Laboratories (London, UK), Synchrotron Radiation Source (SRS, Daresbury, UK), or the European Synchrotron Radiation Facility (ESRF, Grenoble, France) and were processed using the HKL package, (Table 1, Figures 8 and 9)

(Otwinowski et al., *Methods in Enzymol.* 276:307-26 (1997)). The resolution ranged from 2.3-1.7 Å. Since the crystals were isomorphous with wild type PTP1B, its structure was used as a starting model for refinement (Barford et al. (1994), *supra*) using CNS (Brunger et al., *Acta Crystallalog.* D54:905-21 (1998)). Monomer libraries for the sulfinic acid and sulfenyl-amide states of the catalytic cysteine were built using REFMAC as part of the CCP4gui (Collaborative Computational Project No. 4, *Acta Crystallogr. D* 50:670-63 (1994)). Final structures were obtained by an additional one to two rounds of refinement in REFMAC using the appropriate monomer libraries. After a model of the oxidized protein was built, this model was used as the starting model when it resulted in a lower R-factor after the initial rounds of refinement. Final $R_{factors}$ ranged from 18-21% and final R_{free} values of 22 to 23% (Table 1 below).

Table 1a. Crystallographic Data Collection and Refinement Statistics for Oxidation Time Course in 50 μM H_2O_2

Length of oxidation (min)	0 min	40 min	75 min	2 hour	5 hour	16 hour
Oxidation state of Cys215[1]	S^-	75% S^-/25% SN	50% S^-/50% SN	SN	SN	SO_2/SO_3
PTP loop	Closed	Closed/open	Closed/open	Open	Open	Closed
pTyr loop	Closed	Closed/open	Closed/open	Open	Open	Closed
Space group (Z)	$P3_121$	$P3_121$	$P3_121$	$P3_121$	$P3_121$	$P3_121$
Unit Cell Parameters						
a,b (Å)	88.593	88.478	88.349	88.379	88.291	88.701
c (Å)	104.982	104.468	104.186	104.155	104.110	104.688
Z	1	1	1	1	1	1
X-ray source	In-house	In-house	id14eh1	SRS 9.6	SRS 9.6	SRS 9.6
λ (Å)	1.541	1.541	0.933	1.004	1.004	1.004
Resolution (Å)	25.0-2.10	25.00-2.15	50.0-1.7	50.0-1.90	50.0-1.95	50.0-2.0
Observations (N)	172,491	207,986	276,849	491,640	387,847	454,203
Unique (N)	28,289	26,116	51,760	37,560	31,895	32,529
Completeness (%)[2]	99.9 (99.7)	99.6%	99.1%	99.9	98.9 (98.0)	99.3 (97.9)
R_{sym}[2,3]	0.066 (0.378)	0.066 (0.41)	0.053 (.386)	0.040 (0.421)	0.048 (0.303)	0.073 (0.256)
$I/\sigma I$[2]	22.62 (3.33)	26.38 (2.84)	24.00 (1.73)	49.8 (4.70)	46.5 (5.80)	35.88 (4.82)
Refinement						
Resolution range (Å)	76.70-2.10	23.00-2.15	76.70-1.80	43.03-1.90	43.03-1.95	31.78-2.00
Reflections working set	26,846	24,789	41,756	35,694	32,600	30,880
R_{free} set (N) (%)	1443 (5.1%)	1324 (5.1%)	2241 (5.1%)	1922 (5.1%)	1748 (5.1%)	1649 (5.1%)
R_{cryst}[2,4]/R_{free}[2,5]	0.1976/0.2172	0.180/0.222	0.181/0.201	0.213/0.236	0.206/0.231	0.207/0.235
Protein atoms (N)	2289	2289	2289	2289	2289	2290
Solvent atoms (N)	163	140	178	145	154	133
Rmsd bond angles (°)	1.877	2.072	1.663	1.818	1.869	1.932
Rmsd bond lengths (Å)	0.026	0.029	0.019	0.023	0.024	0.028

Table1b: Data for Oxidation of PTP1B Using Equimolar H_2O_2 Prior to Crystallization

Time until data-collection	3-week	3-month
Oxidation state of Cys215[1]	SN	SO_3
PTP loop	Open	Closed
pTyr loop	Open	Closed
Space group (Z)	$P3_121$	$P3_121$
Unit Cell Parameters		
a,b (Å)	88.218	88.368
c (Å)	103.787	104.783
Z	1	1
X-ray source	id14eh1	In-house
λ (Å)	0.933	1.541
Resolution (Å)	50-1.75	50.0-2.40
Observations (N)	308,523	137,296
Unique (N)	43,606	18,467
Completeness (%)[2]	99.5 (99.3)	97.2 (95.9)
R_{sym}[2,3]	0.039 (0.355)	0.086 (0.366)
$I/\sigma I$[2]	26.26 (2.68)	19.79 (3.84)
Refinement		
Resolution range (Å) rfm	76.70-1.80	76.70-2.40
Reflections working set rfm	41389	17,535
R_{free} set (N) (%)	2217 (5.1%)	932 (5.0%)
R_{cryst}[2,4]/R_{free}[2,5] (rfm)	0.204/0.226	0.181/0.227
Protein atoms (N)	2289	2291
Solvent atoms (N)	181	142
Rmsd bond angles (°) rfm	1.785	2.164
Rmsd bond lengths (Å) rfm	0.0200	0.033

Table 1c. Data for Sulfenyl-Amide Reduction Experiment Using DTT or GSH

Length of Oxidation	~12 hours	~12 hours	~16 hours	~16 hours
Length of Reduction/ Reducing agent	O hours	72hours/5mM DTT	O hours	72 hours/ 5mM GSH
Oxidation state of Cys215[1]	SN	S^-	SN	S^-
PTP loop	Open	Closed	Open	Closed
pTyr loop	Open	Closed	Open	Closed
Space group (Z)	$P3_121$	$P3_121$	$P3_121$	$P3_121$
Unit Cell Parameters				
a,b (Å)	88.513	88.513	88.441	88.410
c (Å)	104.180	104.859	103.980	104.626
Z	1	1	1	1
X-ray source	In-house	In-house	In-house	id14eh1
λ (Å)	1.541	1.541	1.541	0.933
Resolution (Å)	25.0-2.2	25.0-2.3	25.0-2.3	50.0-1.90
Observations (N)	179,489	144,827	149,942	227,910
Unique (N)	24,440	21,540	21,226	37,661
Completeness (%) [2]	99.5 (99.3)	99.7 (99.2)	99.1(98.4)	99.6 (98.0)
R_{sym} [2,3]	0.081 (0.447)	0.085 (0.423)	0.80 (0.47)	0.066 (0.176)
$I/\sigma I^2$	19.36 (2.82)	19.10 (3.26)	17.13 (2.49)	26.56 (4.82)
Refinement				
Resolution range (Å)	76.70-2.20	76.70-2.30	76.70-2.30	76.70-1.90
Reflections working set	23204	20444	20144	35730
R_{free} set (N) (%)	1234 (5.0)	1096 (5.1%)	1082 (5.1%)	1931 (5.1%)
R_{cryst} [2,4]/R_{free} [2,5]	0.189/0.229	0.182/0.212	0.188/0.233	0.192/0.215
Protein atoms (N)	2289	2289	2289	2289
Solvent atoms (N)	134	132	121	197
Rmsd bond angles (°)	2.09	2.031	2.215	1.67
Rmsd bond lengths (Å)	0.029	0.028	0.031	0.021

Table 1d. Crystallographic Statistics for Pervanadate Soak and Co-Cystals with 130 μM H_2O_2

Treatment	100μM pervanadate overnight soak	Co-crystals 130μM H_2O_2
Oxidation state of Cys215[1]	SO_3	SN
PTP loop	Closed	Open
pTyr loop	Closed	Open
Space group (Z)	$P3_121$	$P3_121$
Unit Cell Parameters		
a,b (Å)	88.365	88.322
c (Å)	104.764	104.076
Z	1	1
X-ray source	In-house	id14eh1
λ (Å)	1.541	0.933
Resolution (Å)	25.00-2.15	50.0-1.8
Observations (N)	183,671	236,569
Unique (N)		43,303
Completeness (%)[2]	98.1 (96.7)	98.5 (97.5)
R_{sym}[2,3]	0.071 (0.332)	0.053 (0.374)
$I/\sigma I$[2]	25.68 (3.97)	22.57 (2.44)
Refinement		
Resolution range (Å)	76.70-2.15	76.70-1.80
Reflections working set	24,459	41,102
R_{free} set (N) (%)	1305 (5.1%)	2201 (5.1%)
R_{cryst}[2,4] / R_{free}[2,5]	0.185/0.215	0.201/0.223
Protein atoms (N)	2289	2289
Solvent atoms (N)	158	188
Rmsd bond angles (°)	1.894	1.689
Rmsd bond lengths (Å)	0.026	0.020

Table 1 footnotes:

[1]For the oxidation states of the catalytic site cysteine: S^- = reduced cysteine, SN= the sulfenyl-amide bond between C215 and S216, SO_2= sulfinic acid, SO_3=sulfonic acid. The state used for generating the crystallographic statistics listed is highlighted in bold at the top of each table.

[2]Numbers in parentheses refer to the values in the highest resolution shell.

[3]$R_{sym}=\sum_h\sum_i|I(h)-I_i(h)|/\sum_h\sum_i I_i(h)$ where $I_i(h)$ and $I(h)$ are the i[th] and mean measurements of the intensity of reflection h.

[4]$R_{cryst}=\sum_{hkl}\|F_o|-k|F_c\|/\sum_{hkl}|F_o|$ where F_o and F_c are the observed and calculated structure factor amplitudes of reflection h, and k is a weighting factor.

[5] $R_{free} = \sum_{hkl \in T} \| F_o | - k | F_c \| / \sum_{hkl} | F_o |$ where F_o and F_c are the observed and calculated structure factor amplitudes of reflection h, and k is a weighting factor. T is the test set of reflections.

λ: wavelength, rmsd: root mean square deviation, Z: number of molecules in the asymmetric unit.

Reduction of the sulfenyl-amide bond. Crystals prepared as described for the time course were transferred into 4 µl of crystallization buffer with 20 µM H_2O_2 and soaked for 12 hours (prior to reduction with DTT) or 16 hours (prior to reduction with GSH). After the H_2O_2 soak, one crystal was frozen for data collection to verify that it was in the cyclic sulfenyl-amide state. The other three crystals were incubated in 40 µl of crystallization buffer with either DTT (5 mM) or GSH (5 mM) for 72 hours before data collection.

Crystals of PTP1B with pervanadate. Crystals were soaked in crystallization well solution without DTT and with 50 µM pervanadate. The pervanadate was a 1:1 ratio of sodium orthovanadate and H_2O_2 at room temperature for 20 min. The crystals were soaked ~14 hours.

Analysis of PTP1B in solution using mass spectrometry. PTP1B D181A and C215S mutant (56 µM) was incubated with the indicated concentrations of H_2O_2 for 10 minutes in 50 mM Hepes, pH 7.5, 1 mM EDTA, 200 µM DTT. One µL was digested with trypsin in 50 mM ammonium bicarbonate, pH 8.0, and analyzed using matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry. Ten µL were boiled for 10 minutes in SDS-loading buffer and analyzed by SDS-PAGE. To reversibly oxidize PTP1B (pulse-chase experiment), 30 µL 'heavy' $H_2{}^{18}O_2$ (2% stock solution, Icon 19 Ox Bow Lane, Summit, NJ) was added to an equal volume of 26 µM PTP1B in degassed buffer (50 mM Hepes, pH 7.5, 1 mM EDTA, 100 µM DTT) giving final concentrations of between 5 and $5x10^4$ µM. At 30 minutes, 10 µL of the PTP1B mixture were removed and chased with "light" $H_2{}^{16}O_2$ (>100 fold excess) for two hours and then trypsinized. Twenty µl were removed to assay enzyme activity (% inhibition) using 4-nitrophenyl phosphate (pNPP) as substrate. The remaining 30 µl of sample were incubated with DTT (10 mM) and catalase (10 units) for two hours, and the

recovered enzyme activity was measured using pNPP as substrate (% recovery). For trypsinolysis, PTP1B was diluted with 50 mM ammonium bicarbonate, pH 8.0, 5 mM DTT, and 0.3 μg of sequencing grade trypsin and incubated at 37 °C for 12-16 hours. One μL of digest was mixed with saturated α-cyano-4-hydroxycinnamic acid and analyzed with a Voyager DE-RP mass spectrometer. Internal reference standards were used for calibration.

Oxidation induced disruption of PTP1B-IRK interactions. PTP1B D181A (12 μg) diluted in 50 mM Tris, pH 7.6, 0.1 mM DTT was oxidized with increasing concentrations of H_2O_2 at room temperature in a total volume of 400 μl. After 10 minutes of oxidation, kinase buffer (50 mM Tris pH 7.6, 4 mM $MnCl_2$, 10 mM $MgCl_2$, 100 μM ATP) containing purified autophosphorylated insulin receptor (IR, 2 μg) and γ-^{32}P-ATP was added to each sample (1 ml final volume). After 20 minutes, the kinase reaction was terminated by addition of EDTA, PTP1B was immunoprecipitated with FG6 antibody, and proteins in the immunocomplexes were resolved by SDS-PAGE.

Similar experimental methods may be carried out following the above-described materials and methods to create and test PTP-SN or PTP-SS forms of any PTP including, without limitation, the classical PTPs as described by Andersen et al. (2001) and Andersen et al. (2004); PTP-eta, PTP-epsilon, DEP-1 (CD148), SHP2, SHP1, cdc25 (a, b, or c), cdc14a, cdc14b, DSP-2, DSP-3, DSP-4, DSP-5, DSP-6, DSP-7, DSP-8, DSP-9, DSP-10, DSP-11, DSP-12, DSP-13, DSP-14, DSP-15, DSP-16, DSP-17, DSP-18, CD45, etc. Other methods that do not require the use of a crystalline PTP in order to accomplish oxidation to form the PTP-SN or PTP-SS polypeptide may also be used.

PTPs, whether in isolated or purified form or in whole cells, are subjected to an oxidizing agent such as hydrogen peroxide under conditions and for a time sufficient to permit the formation of the PTP-SN or PTP-SS state. For example, a selected PTP (56 μM) is incubated with 50 μM H_2O_2 for 10 minutes in 50 mM Hepes, pH 7.5, 1 mM EDTA, 200 μM DTT. One μL is digested with trypsin in 50 mM ammonium bicarbonate, pH 8.0, and analyzed using MALDI-TOF mass spectrometry. Ten microliters are boiled for 10 minutes in SDS-loading buffer and analyzed by SDS-PAGE.

To reversibly oxidize the PTP (pulse-chase experiment), 30 μL 'heavy' $H_2{}^{18}O_2$ (2% stock solution, Icon 19 Ox Bow Lane, Summit, NJ, USA) is added to an equal volume of 26 μM PTP1B in degassed buffer (50 mM Hepes, pH 7.5, 1 mM EDTA, 100 μM DTT) giving final concentrations of between 5 and $5x10^4$ μM. At 30 minutes, 10 μL of the selected PTP mixture is removed and chased with "light" $H_2{}^{16}O_2$ (>100 fold excess) for two hours and then trypsinized; 20 μl is removed to assay enzyme activity (% inhibition) using pNPP as substrate. The remaining 30 μl of the sample are incubated with DTT (10 mM) and catalase (10 units) for two hours, and the recovered enzyme activity is measured using pNPP as substrate (% recovery). For trypsinolysis, the selected PTP is diluted with 50 mM ammonium bicarbonate, pH 8.0, 5 mM DTT, and 0.3 μg of sequencing grade trypsin and incubated at 37 °C for 12-16 hours. One μL of digest is mixed with saturated α-cyano-4-hydroxycinnamic acid and analyzed with a mass spectrometer.

EXAMPLE 2

X-RAY CRYSTALLOGRAPHY ANALYSIS OF PTP1B DOUBLE MUTANT

A PTP1B double mutant was prepared by substituting an alanine residue for the catalytic cysteine residue at position 215 and substituting an alanine residue for the serine residue at position 216 of the wildtype PTP1B using standard site-directed mutagenesis techniques known in the art. The double mutant PTP1B was analyzed by X-ray crystallography using techniques similar to those described in Example 1 for solving the crystal structure of wildtype PTP1B.

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

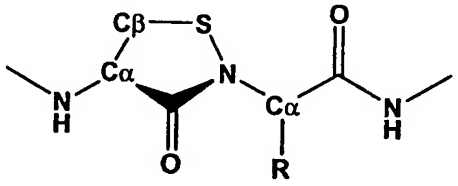
CLAIMS

What is claimed is:

1. An isolated polypeptide comprising the amino acid sequence –C-$(X)_5$-R- (SEQ ID NO:1), wherein C is cysteine, R is arginine, and X is any amino acid residue, and wherein a sulfur atom of the cysteine is covalently linked to a main-chain nitrogen atom of an adjacent C-terminal amino acid residue.

2. An isolated protein tyrosine phosphatase polypeptide in a cyclic sulfenyl-amide form (PTP-SN).

3. An isolated polypeptide comprising the sequence -Cys-$(X)_5$-Arg- (SEQ ID NO:1), wherein X is any amino acid residue, and wherein the cysteine residue and the adjacent C-terminal amino acid residue in SEQ ID NO:1 form the following chemical structure



wherein R is the amino acid side chain of the adjacent C-terminal amino acid residue.

4. The polypeptide according to any one of claims 1-3, wherein the polypeptide is selected from the group consisting of PTP1B comprising the amino acid sequence set forth in any one of SEQ ID NOS:24, 26, and 30; cdc14a comprising the amino acid sequence set forth in any one of SEQ ID NOS:85, 87, and 89; cdc14b comprising the amino acid sequence set forth in any one of SEQ ID NOS:91 and 93; cdc25a comprising the amino acid sequence set forth in any one of SEQ ID NOS:67 and 69; cdc25b

comprising the amino acid sequence set forth in any one of SEQ ID NOS:77 and 79; cdc25c comprising the amino acid sequence set forth in any one of SEQ ID NOS:81 and 83; DSP-3/JSP-1 comprising the amino acid sequence set forth in SEQ ID NO:97; and DEP-1 comprising the amino acid sequence set forth in any one of SEQ ID NOS:38 and 40.

5. The polypeptide according to any one of claims 1-3, wherein the polypeptide is PTP1B comprising the amino acid sequence set forth in any one of SEQ ID NOS:24, 26, and 30.

6. An isolated protein tyrosine phosphatase (PTP) enzyme comprising a sequence [I/V]HCXAGXXR[S/T]G (SEQ ID NO:106), wherein X is any amino acid, and wherein cysteine in SEQ ID NO:106 and the adjacent C-terminal residue together form a cyclic sulfenyl-amide group between the sulfur atom of the cysteine and the main-chain nitrogen atom of the adjacent C-terminal residue.

7. The PTP according to claim 6, wherein the PTP is selected from the group consisting of (a) PTP1B comprising the amino acid sequence set forth in any one of SEQ ID NOS:24, 26, and 30 and (b) DEP-1 comprising the amino acid sequence set forth in any one of SEQ ID NOS:38 and 40.

8. The PTP according to claim 6 wherein the PTP is PTP1B comprising the amino acid sequence set forth in any one of SEQ ID NOS:24, 26, and 30.

9. A method of making a protein tyrosine phosphatase in a cyclic sulfenyl-amide form (PTP-SN) comprising subjecting a biological sample comprising a PTP that comprises the sequence C-$(X)_5$-R (SEQ ID NO:1), wherein X is any amino acid, to oxidation conditions for a time and under conditions sufficient to induce the cysteine residue of SEQ ID NO:1 to form a cyclic sulfenyl-amide with the adjacent C-terminal residue.

10. A method for identifying a compound that hinders reduction of a cyclic sulfenyl-amide protein tyrosine phosphatase (PTP-SN) comprising:

(a) introducing a PTP-SN to a test compound to form a composition;

(b) adding a reducing agent to the composition of (a) under conditions and for a time sufficient to permit binding of the test compound to the PTP-SN; and

(c) analyzing the composition to determine the presence or absence of PTP-SN.

11. The method of claim 10, wherein the reducing agent is selected from the group consisting of beta-mercaptoethanol, dithiothreitol (DTT), dithioerythritol (DTE), glutathione, and a phosphine.

12. The method according to claim 10, wherein the step of analyzing comprises performing a functional assay on the composition to determine PTP catalytic activity.

13. A method for identifying a compound that binds to a protein tyrosine phosphatase sulfenyl-amide form (PTP-SN) comprising:

(a) contacting a PTP-SN with a test compound; and

(b) determining binding of the compound to the PTP-SN, thereby identifying a compound that binds to the PTP-SN.

14. The method of claim 13 wherein the compound does not bind to a PTP-SN that has been converted to a catalytically active PTP by reducing conditions.

15. The method of claim 13 wherein the step of determining binding comprises performing X-ray crystallographic analysis.

16. The method of either claim 10 or claim 13 wherein the compound stabilizes the PTP-SN in the oxidized state.

17. The method according to either claim 10 or claim 13, wherein the PTP is PTP1B comprising the amino acid sequence set forth in any one of SEQ ID NOS:24, 26, and 30.

18. The method according to either claim 10 or claim 13, wherein the PTP is selected from the group consisting of PTP1B comprising the amino acid sequence set forth in any one of SEQ ID NOS:24, 26, and 30; cdc14a comprising the amino acid sequence set forth in any one of SEQ ID NOS:85, 87, and 89; cdc14b comprising the amino acid sequence set forth in any one of SEQ ID NOS:91 and 93; cdc25a comprising the amino acid sequence set forth in any one of SEQ ID NOS:67 and 69; cdc25b comprising the amino acid sequence set forth in any one of SEQ ID NOS:77 and 79; cdc25c comprising the amino acid sequence set forth in any one of SEQ ID NOS:81 and 83; DSP-3/JSP-1 comprising the amino acid sequence set forth in SEQ ID NO:97; and DEP-1 comprising the amino acid sequence set forth in any one of SEQ ID NOS:38 and 40.

19. A method for identifying a compound that modulates or hinders reduction of a cyclic sulfenyl-amide protein tyrosine phosphase-1B (PTP1B-SN) comprising:

(a) obtaining crystalline PTP1B-SN;

(b) introducing a test compound to the crystalline PTP1B-SN under conditions and for a time sufficient to permit binding of the test compound to the PTP1B-SN; and

(c) analyzing the crystalline PTP1B-SN to determine whether the test compound binds thereto.

20. A method for identifying a compound that hinders reduction of a cyclic sulfenyl-amide protein tyrosine phosphase-1B (PTP1B-SN) comprising:

(a) introducing a test compound to the PTP1B-SN to form a composition;

(b) adding a reducing agent to the composition of (a), under conditions and for a time sufficient to permit binding of the test compound to the PTP1B-SN; and

(c) analyzing the composition to determine the presence or absence of PTP1B-SN.

21. A double mutant protein tyrosine phosphatase (PTP) polypeptide having the amino acid sequence –CS(X)$_4$-R- set forth in SEQ ID NO:109, wherein X is any amino acid, said mutant PTP comprising a substitution of the cysteine in SEQ ID NO:1 and a substitution of the amino acid that is the adjacent C-terminal residue to the cysteine residue.

22. The double mutant PTP of claim 21 wherein the catalytic domain of the double mutant PTP possesses a three-dimensional structure that is substantially similar to the three-dimensional structure of the catalytic domain of the corresponding PTP-SN.

23. A double mutant protein tyrosine phosphatase (PTP) polypeptide having the amino acid sequence -H-C-S-X-G-X-G-R-X-G- set forth in SEQ ID NO:21, wherein X is any amino acid, said mutant PTP comprising (a) a substitution of the cysteine in SEQ ID NO:21, and (b) a substitution of the serine that is adjacent to the cysteine residue.

24. The double mutant PTP of claim 23 wherein the catalytic domain of the double mutant PTP possesses a three-dimensional structure that is substantially similar to the three-dimensional structure of the catalytic domain of the corresponding PTP-SN.

25. The double mutant PTP polypeptide according to either claim 21 or claim 23, wherein the PTP is selected from the group consisting of PTP1B comprising the amino acid sequence set forth in any one of SEQ ID NOS:24, 26, and 30 and DEP-1 comprising the amino acid sequence set forth in any one of SEQ ID NO:38 and 40.

26. The double mutant PTP according to claim 21 wherein the cysteine residue is substituted with an alanine residue.

27. The double mutant PTP according to claim 21 wherein the adjacent C-terminal residue is substituted with an alanine residue.

28. The double mutant PTP according to claim 21 wherein the cysteine residue is substituted with an alanine residue and wherein the adjacent C-terminal residue is a serine residue that is substituted with an alanine residue.

29. A double mutant protein tyrosine phosphatase-1B (PTP1B) polypeptide comprising the amino acid sequence of SEQ ID NO:109 in which the cysteine in SEQ ID NO:109 is substituted and the serine in SEQ ID NO:109 is substituted, wherein the cysteine is located at position number 215 in any one of SEQ ID NOS:24, 26, and 30 and the serine is located at position number 216 in any one of SEQ ID NOS:24, 26, and 30, and wherein the double mutant PTP1B is at least 80% identical to the amino acid sequence set forth in in any one of SEQ ID NOS:24, 26, and 30.

30. The double mutant of claim 29 wherein the double mutant PTP1B is at least 90% identical to the amino acid sequence set forth in in any one of SEQ ID NOS:24, 26, and 30.

31. The double mutant of claim 29 wherein the double mutant PTP1B is at least 95% identical to the amino acid sequence set forth in in any one of SEQ ID NOS:24, 26, and 30.

32. The double mutant of claim 29 wherein the double mutant PTP1B is at least 99% identical to the amino acid sequence set forth in in any one of SEQ ID NOS:24, 26, and 30.

33. The double mutant PTP according to claim 29, wherein cysteine located at position 215 is substituted with a alanine residue, and wherein serine located at position 216 is substituted with an alanine residue.

34. The double mutant PTP according to claim 29 comprising the amino acid sequence set forth in SEQ ID NO:110.

35. An antibody, or an antigen-binding fragment thereof, that binds to at least one polypeptide selected from the group consisting of

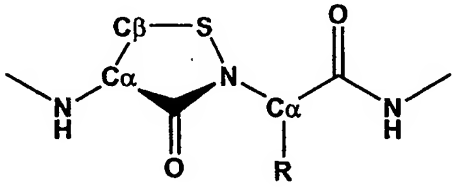
(a) double mutant protein tyrosine phosphatase (PTP) polypeptide having the amino acid sequence $-CS(X)_4-R-$ set forth in SEQ ID NO:109, wherein X is any amino acid, said mutant PTP comprising a substitution of the cysteine in SEQ ID NO:1 and a substitution of an amino acid that is an adjacent C-terminal residue to the cysteine residue; wherein the catalytic domain of the double mutant PTP possesses a three-dimensional structure that is substantially similar to the three-dimensional structure of the catalytic domain of the corresponding PTP-SN;

(b) double mutant protein tyrosine phosphatase (PTP) polypeptide having the amino acid sequence -H-C-S-X-G-X-G-R-X-G- set forth in SEQ ID NO:21, wherein X is any amino acid, said mutant PTP comprising (a) a substitution of the cysteine in SEQ ID NO:21, and (b) a substitution of serine that is adjacent to the cysteine residue; wherein the catalytic domain of the double mutant PTP possesses a three-dimensional

structure that is substantially similar to the three-dimensional structure of the catalytic domain of the corresponding PTP-SN;

(c) a PTP-SN polypeptide comprising comprising the amino acid sequence –C-$(X)_5$-R- (SEQ ID NO:1), wherein C is cysteine, R is arginine, and X is any amino acid residue, and wherein a sulfur atom of the cysteine is covalently linked to a main-chain nitrogen atom of an adjacent C-terminal amino acid residue; and

(d) a PTP-SN polypeptide comprising the sequence Cys-$(X)_5$-Arg (SEQ ID NO:1), wherein X is any amino acid residue, and wherein the cysteine residue and an adjacent C-terminal amino acid residue in SEQ ID NO:1 form the following chemical structure



wherein R is the amino acid side chain of the adjacent C-terminal amino acid residue.

36. The antibody of claim 35 wherein the antibody or antigen binding fragment thereof binds to at least two polypeptides.

37. The antibody of claim 35 wherein the antibody or antigen binding fragment thereof binds to at least one double mutant PTP polypeptide and to at least one PTP-SN polypeptide.

38. The antibody according to claim 35 wherein the antibody is a polyclonal antibody or a monoclonal antibody.

39. The antibody according to claim 35 wherein the antigen-binding fragment is selected from the group consisting of a Fab, a Fab', a $F(ab')_2$, a Fv, and a Fd fragment.

40. The antibody according to claim 35 wherein the antibody is selected from the group consisting of a chimeric antibody, a humanized antibody, and a single chain antibody.

41. The antibody according to claim 38 wherein the monoclonal antibody is selected from the group consisting of a mouse monoclonal antibody, a human monoclonal antibody, a rat monoclonal antibody, and a hamster monoclonal antibody.

42. A hybridoma cell that produces the monoclonal antibody according to claim 38.

43. A host cell that expresses the antibody according to any one of claims 35-41.

44. A composition comprising an antibody, or antigen-binding fragment thereof, according to any one of claims 35-41 and a physiologically acceptable carrier.

45. A method for identifying an agent that binds specifically to a double mutant protein tyrosine phosphatase (PTP) polypeptide comprising (a) contacting a double mutant PTP according to either claim 21 or claim 23 with a candidate agent under conditions and for a time sufficient to permit interaction between the mutant PTP and the candidate agent; (b) contacting the corresponding wildtype PTP polypeptide with the candidate agent under conditions and for a time sufficient to permit interaction between the wildtype PTP and the candidate agent; (c) comparing the level of binding of the candidate agent to the mutant PTP with the level of binding of the candidate agent to the wildtype

PTP, wherein an increased level of binding to the mutant PTP relative to the level of binding to the wildtype PTP indicates that the agent specifically binds to the mutant PTP polypeptide.

46. A method for identifying an agent that alters reduction of a protein tyrosine phosphatase sulfenyl-amide form (PTP-SN) comprising: (a) contacting a double mutant PTP polypeptide according to either claim 21 or claim 23 with a candidate agent under conditions and for a time sufficient to permit interaction between the mutant PTP and the candidate agent; (b) contacting the corresponding wildtype PTP polypeptide with the candidate agent under conditions and for a time sufficient to permit interaction between the wildtype PTP and the candidate agent; (c) determining a level of binding of the candidate agent to the mutant PTP; (d) determining a level of binding of the candidate agent to the wildtype PTP; and (e) comparing the level of binding of the candidate agent to the mutant PTP relative to the level of binding of the candidate agent to the wildtype PTP, wherein an increased or decreased level of binding of the candidate agent to the mutant PTP indicates that the agent alters reduction of a PTP-SN.

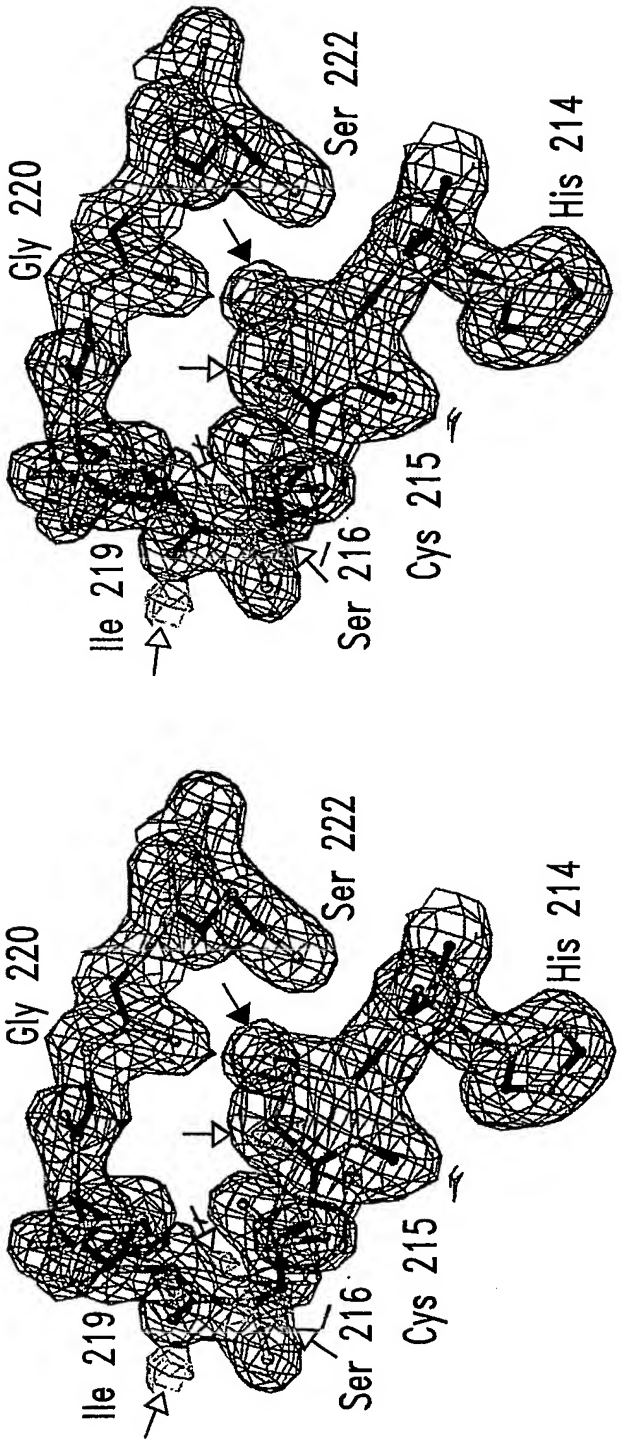


FIG. 1A

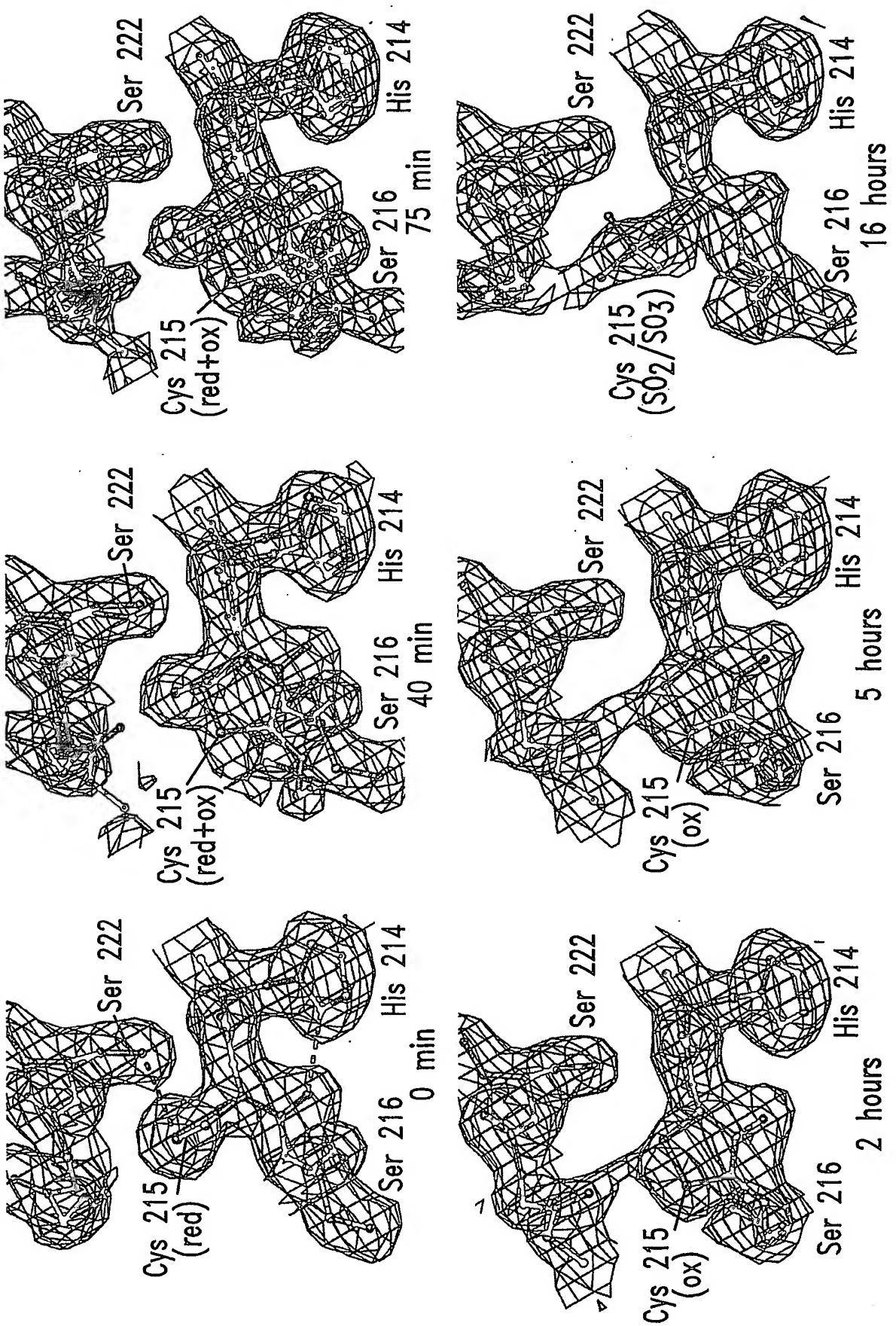


FIG. 1B

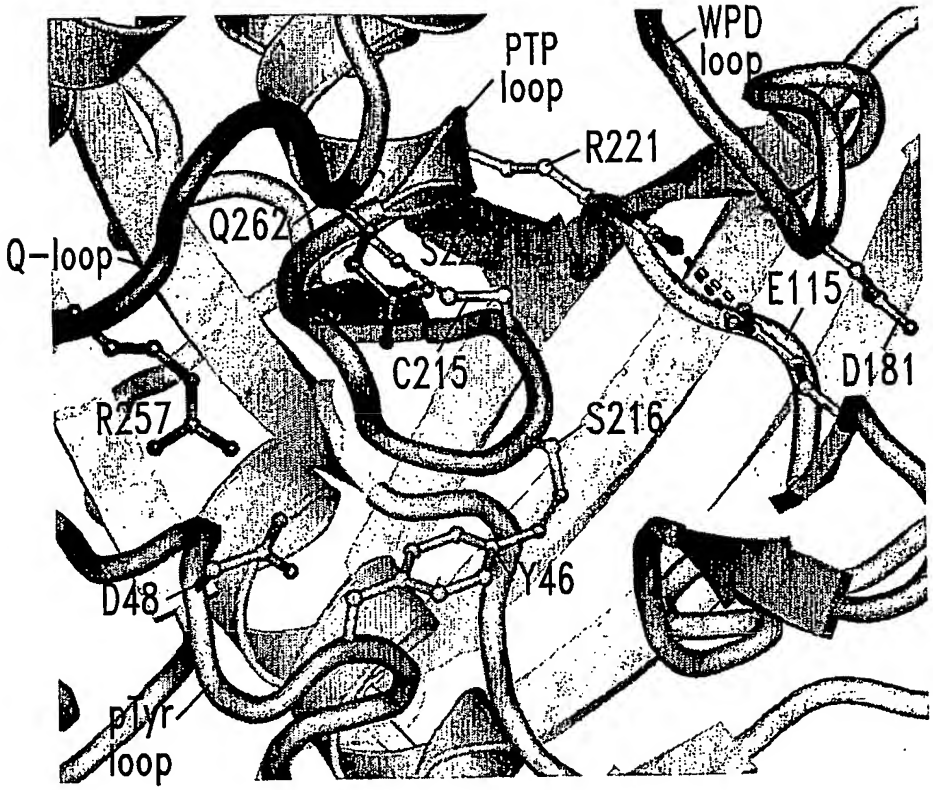


FIG. 2A

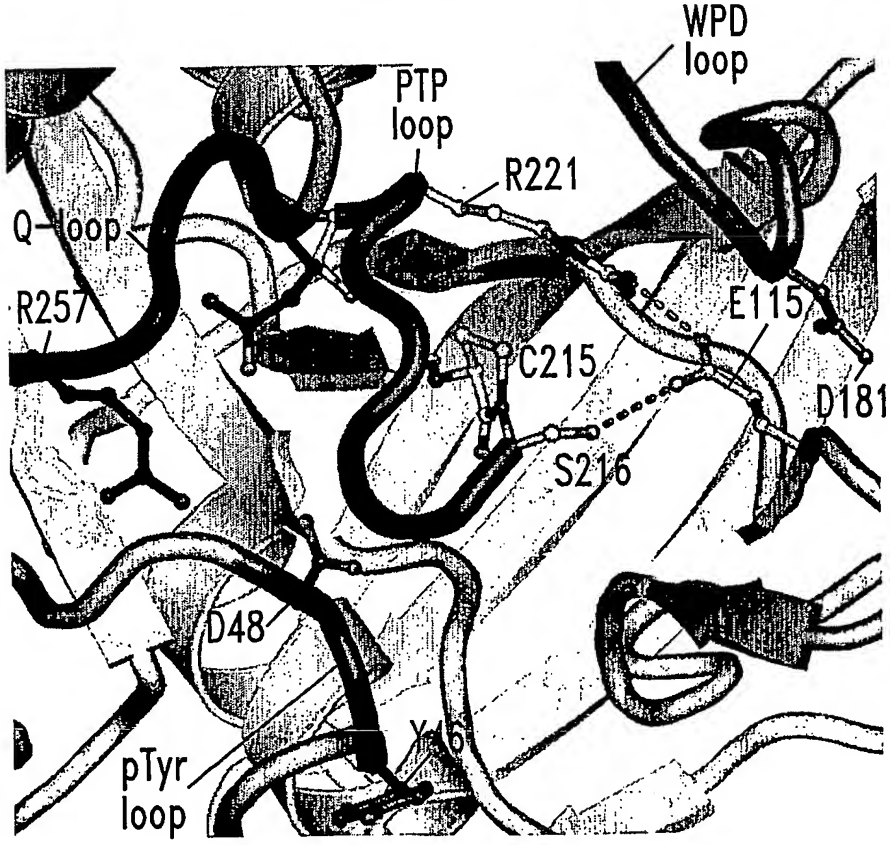


FIG. 2B

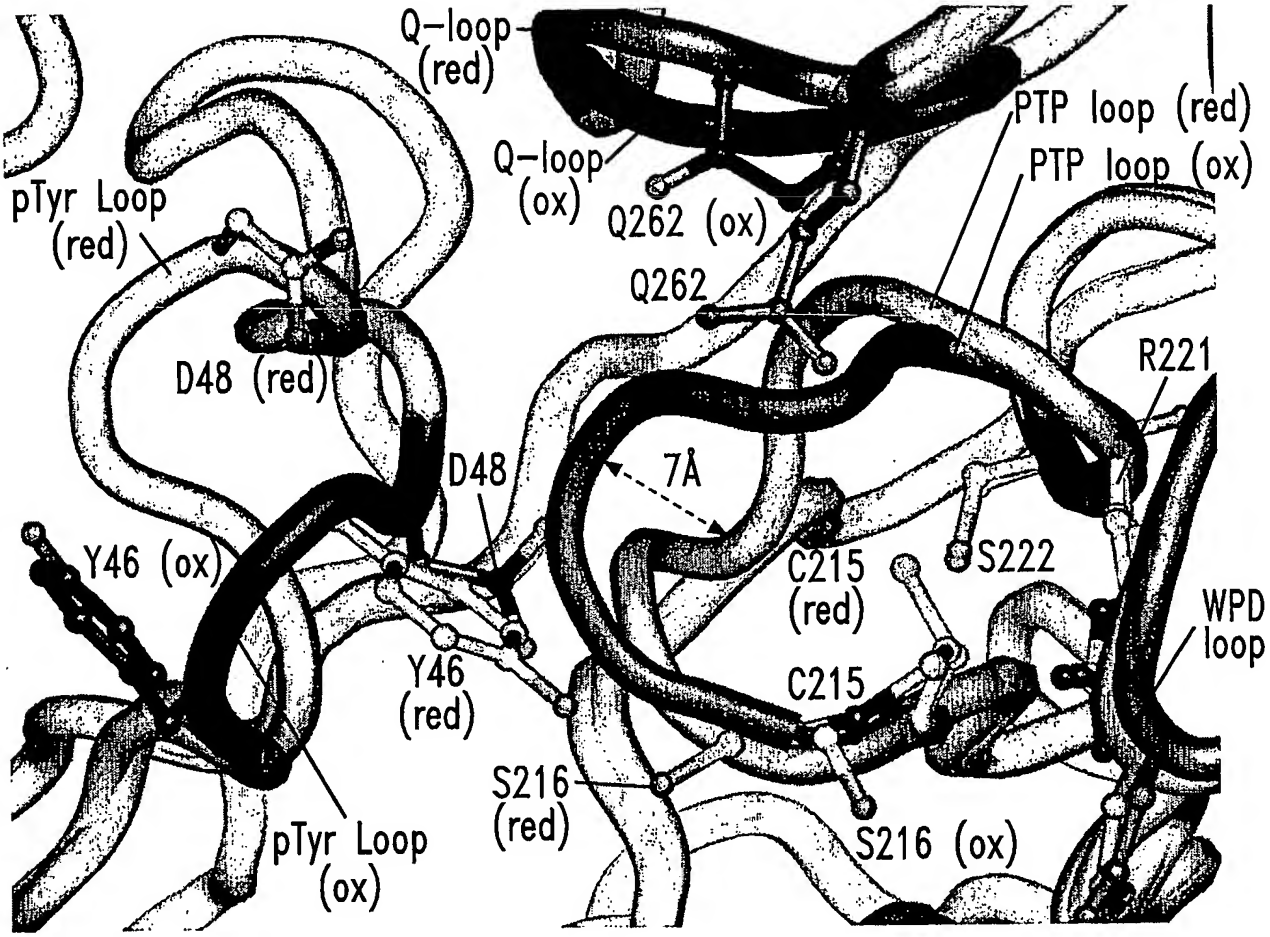


FIG. 2C

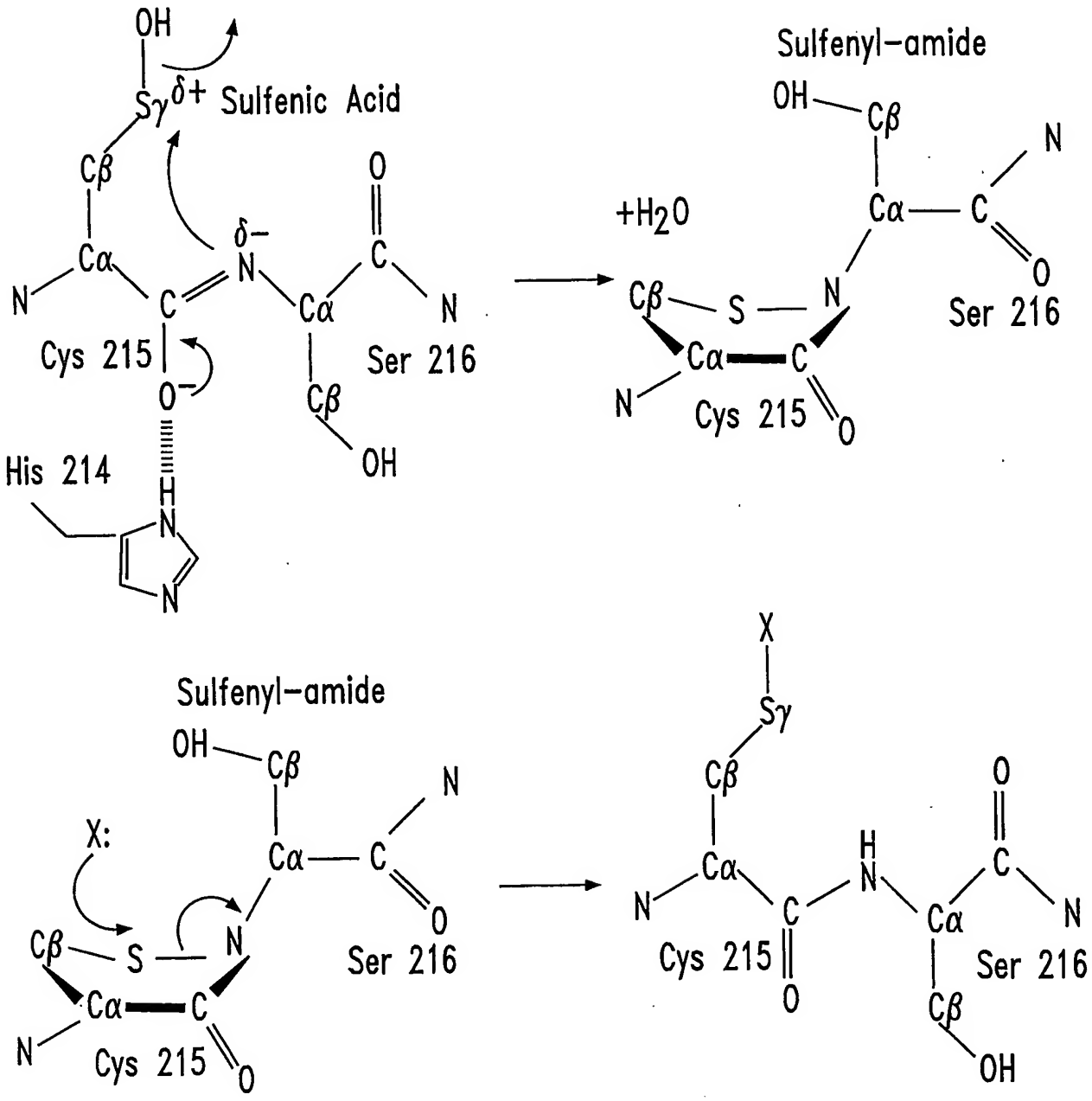

OH
Sγ δ+
Sulfenic Acid
Cβ
Cα
N
C
δ−
N
O
C
N
Cys 215
O−
Cα
Ser 216
Cβ
OH
His 214
H
N
N
Sulfenyl-amide
OH
Cβ
N
+H2O
Cα
C
O
Cβ
S
N
Ser 216
Cα
C
N
Cys 215
O
Sulfenyl-amide
OH
Cβ
N
X:
Cα
C
O
Cβ
S
N
Ser 216
Cα
C
N
Cys 215
O
X
Sγ
Cβ
O
Cα
H
N
C
N
Cα
N
C
Cys 215
O
Ser 216
Cβ
OH

FIG. 2D

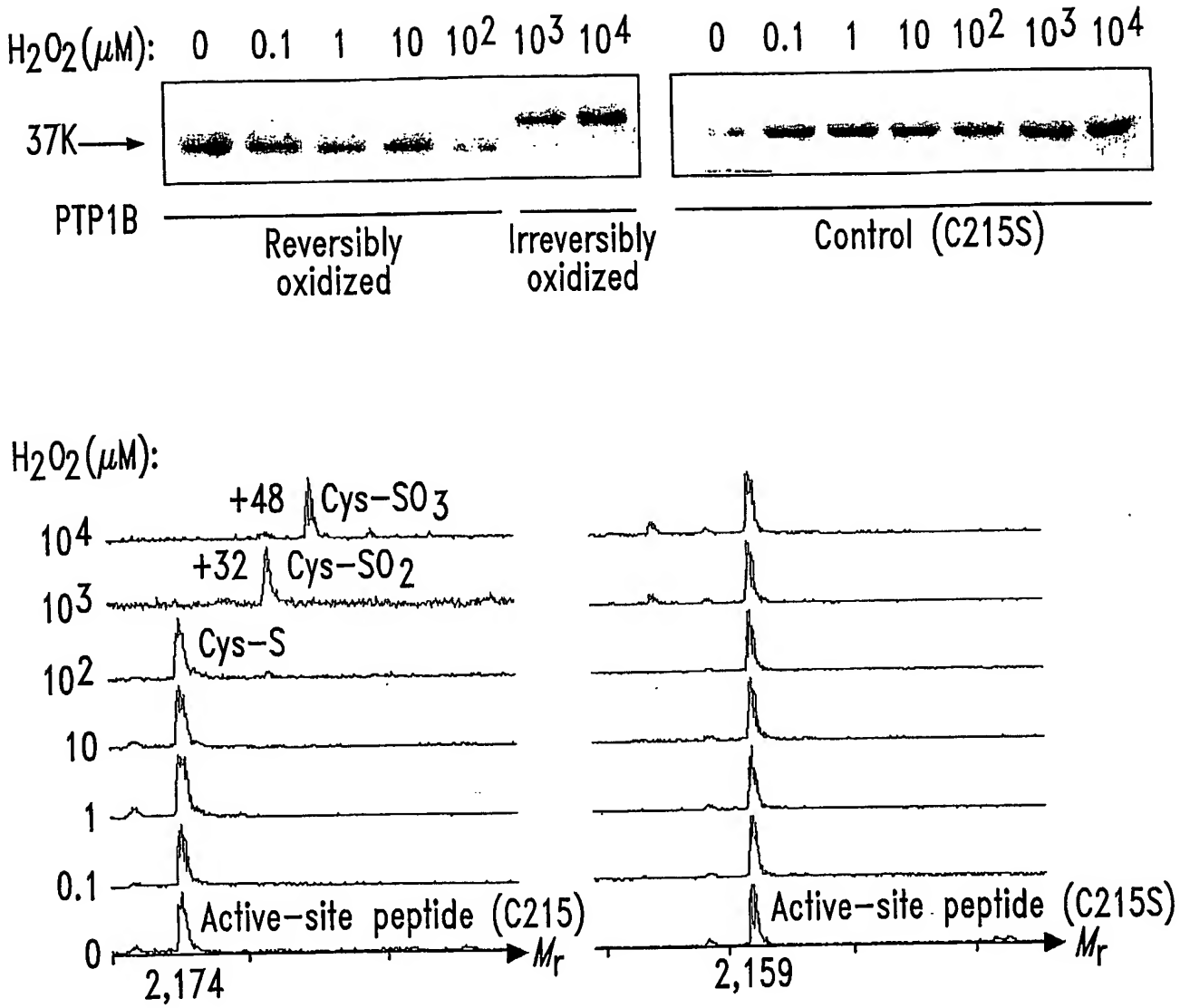

H2O2(μM): 0 0.1 1 10 10^2 10^3 10^4
37K
PTP1B
Reversibly oxidized
Irreversibly oxidized
0 0.1 1 10 10^2 10^3 10^4
Control (C215S)
H2O2(μM):
+48 Cys–SO3
+32 Cys–SO2
Cys–S
10^4
10^3
10^2
10
1
0.1
0
Active–site peptide (C215)
Mr
2,174
Active–site peptide (C215S)
Mr
2,159

FIG. 3A

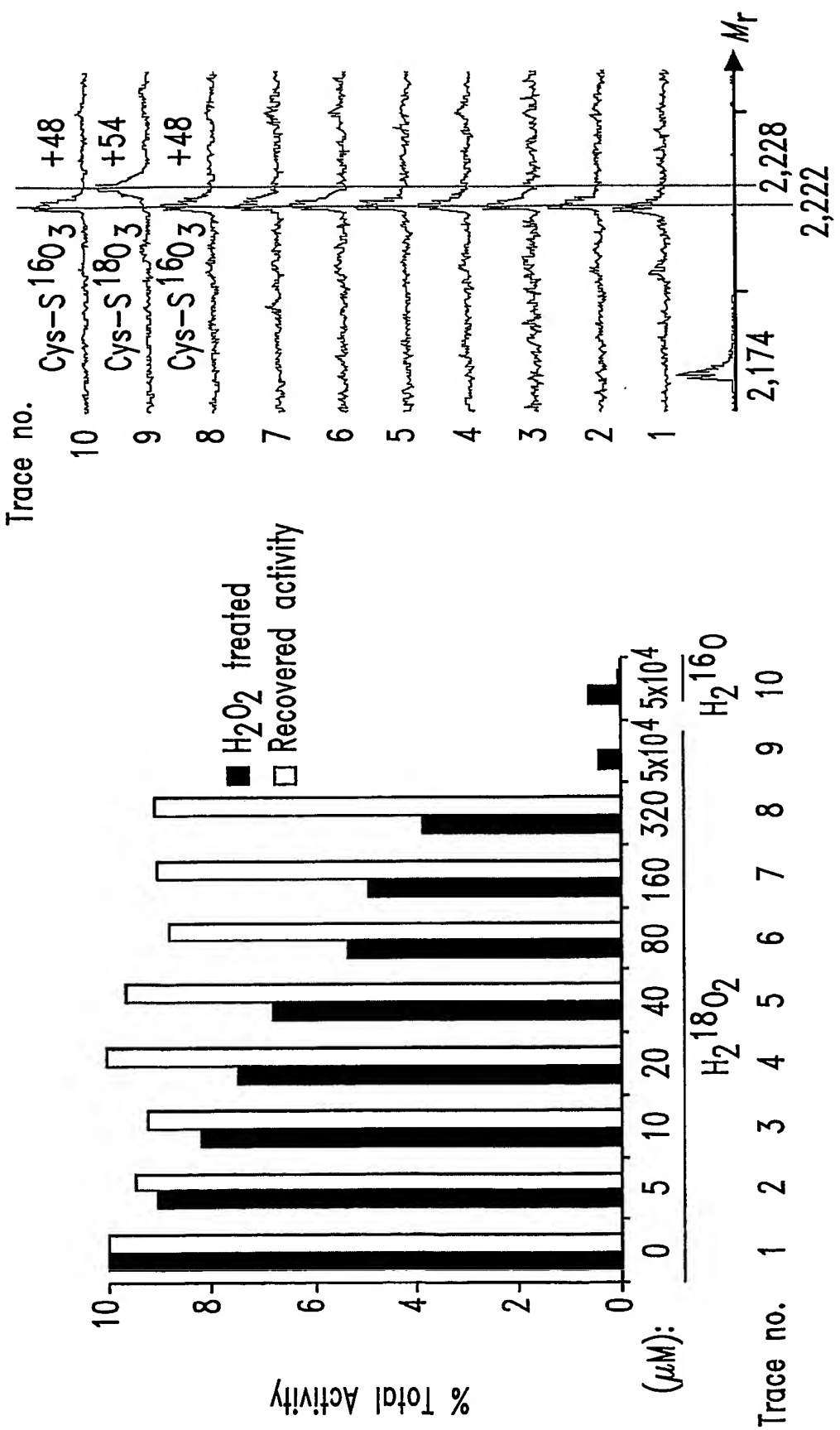


FIG. 3B

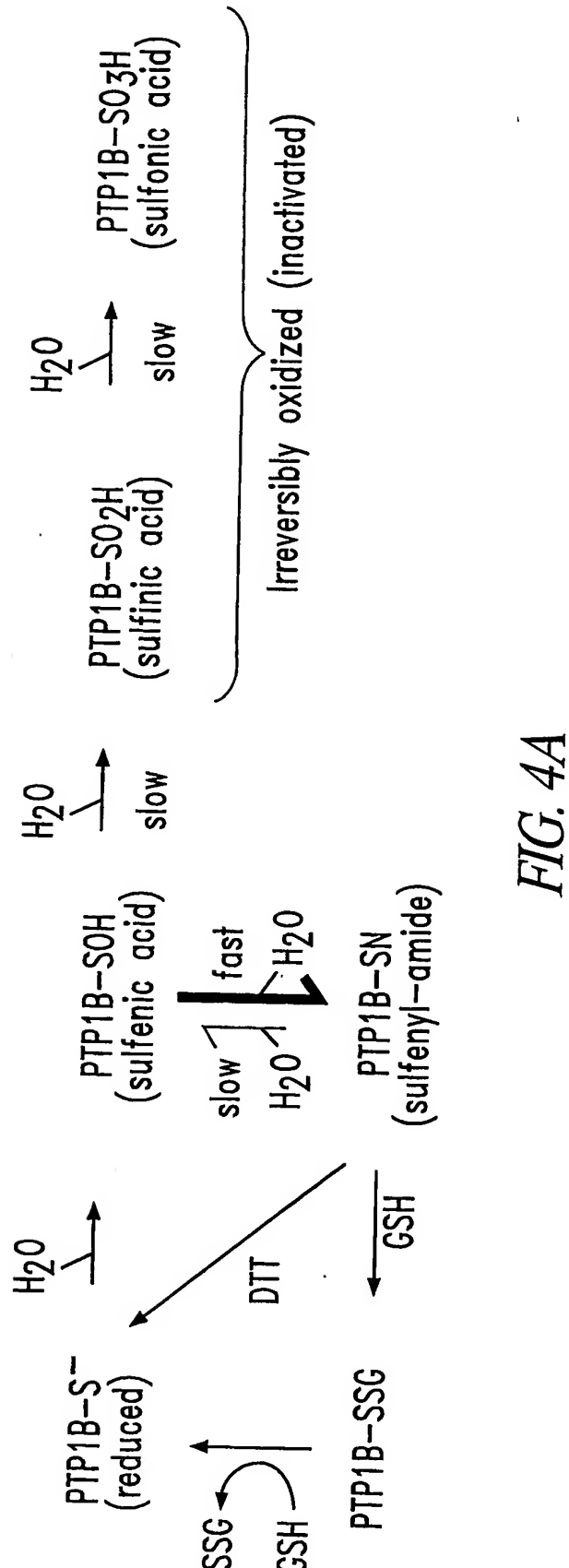

PTP1B-S-
(reduced)
H2O
PTP1B-SOH
(sulfenic acid)
slow
PTP1B-SO2H
(sulfinic acid)
slow
H2O
PTP1B-SO3H
(sulfonic acid)
slow
H2O
fast
H2O
PTP1B-SN
(sulfenyl-amide)
DTT
GSH
PTP1B-SSG
GSSG
GSH
Irreversibly oxidized (inactivated)

FIG. 4A

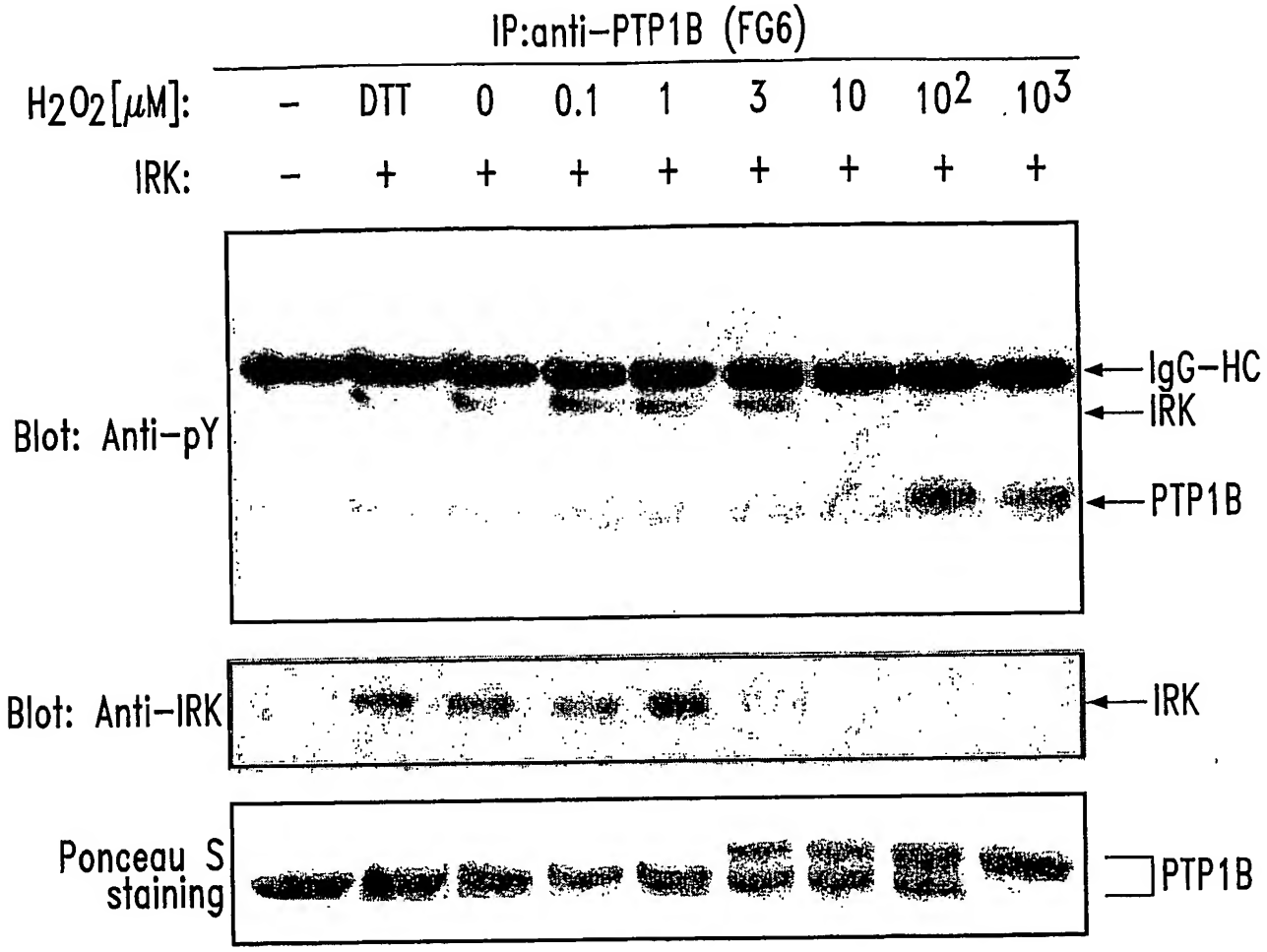


FIG. 4B

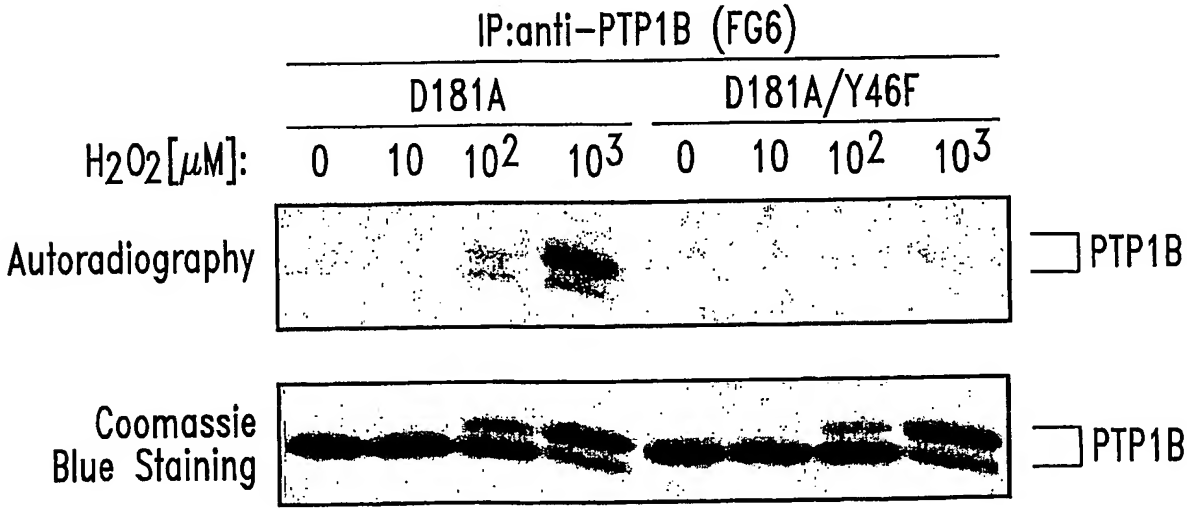


FIG. 4C

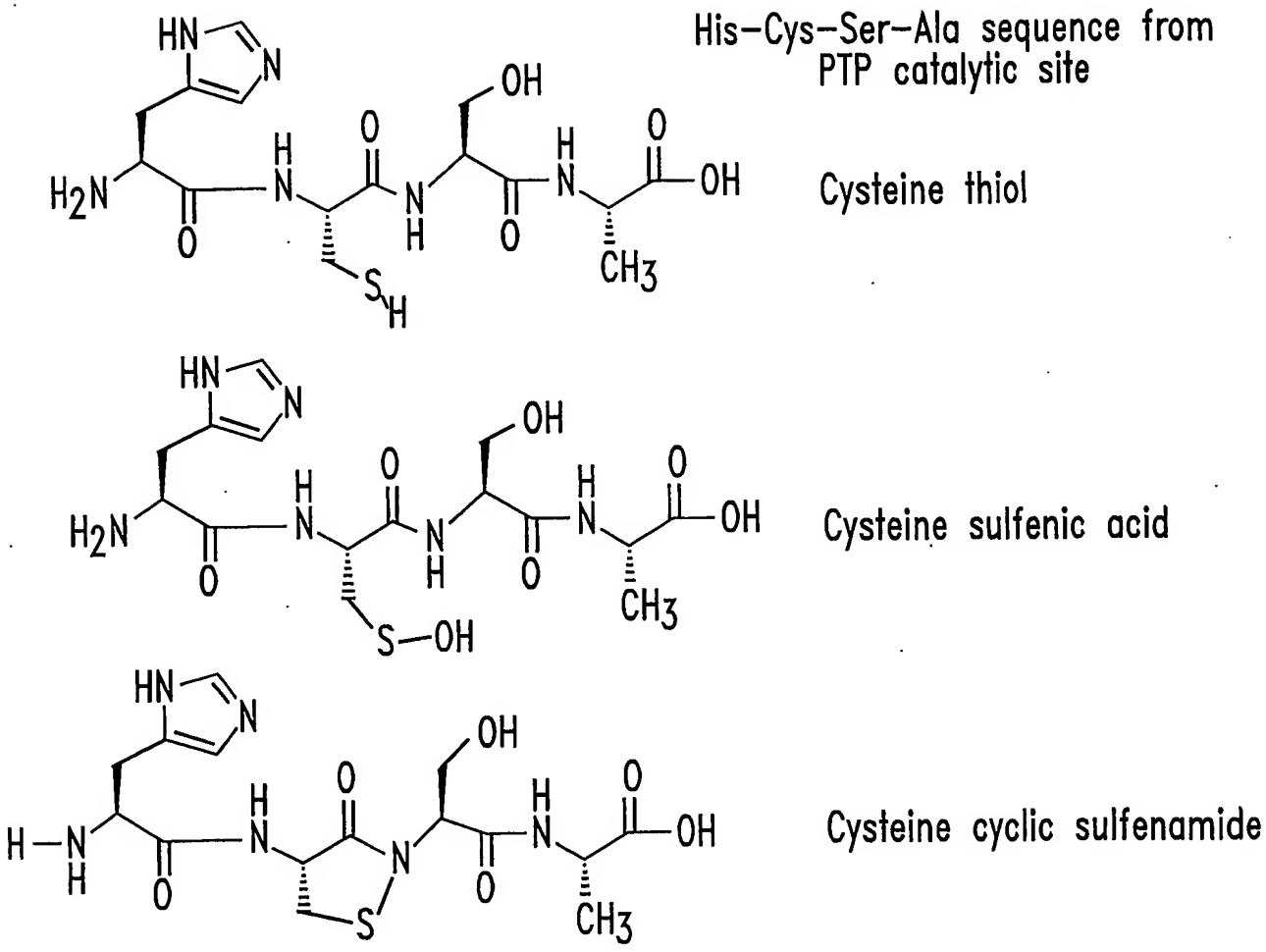

His–Cys–Ser–Ala sequence from PTP catalytic site
Cysteine thiol
Cysteine sulfenic acid
Cysteine cyclic sulfenamide

FIG. 5

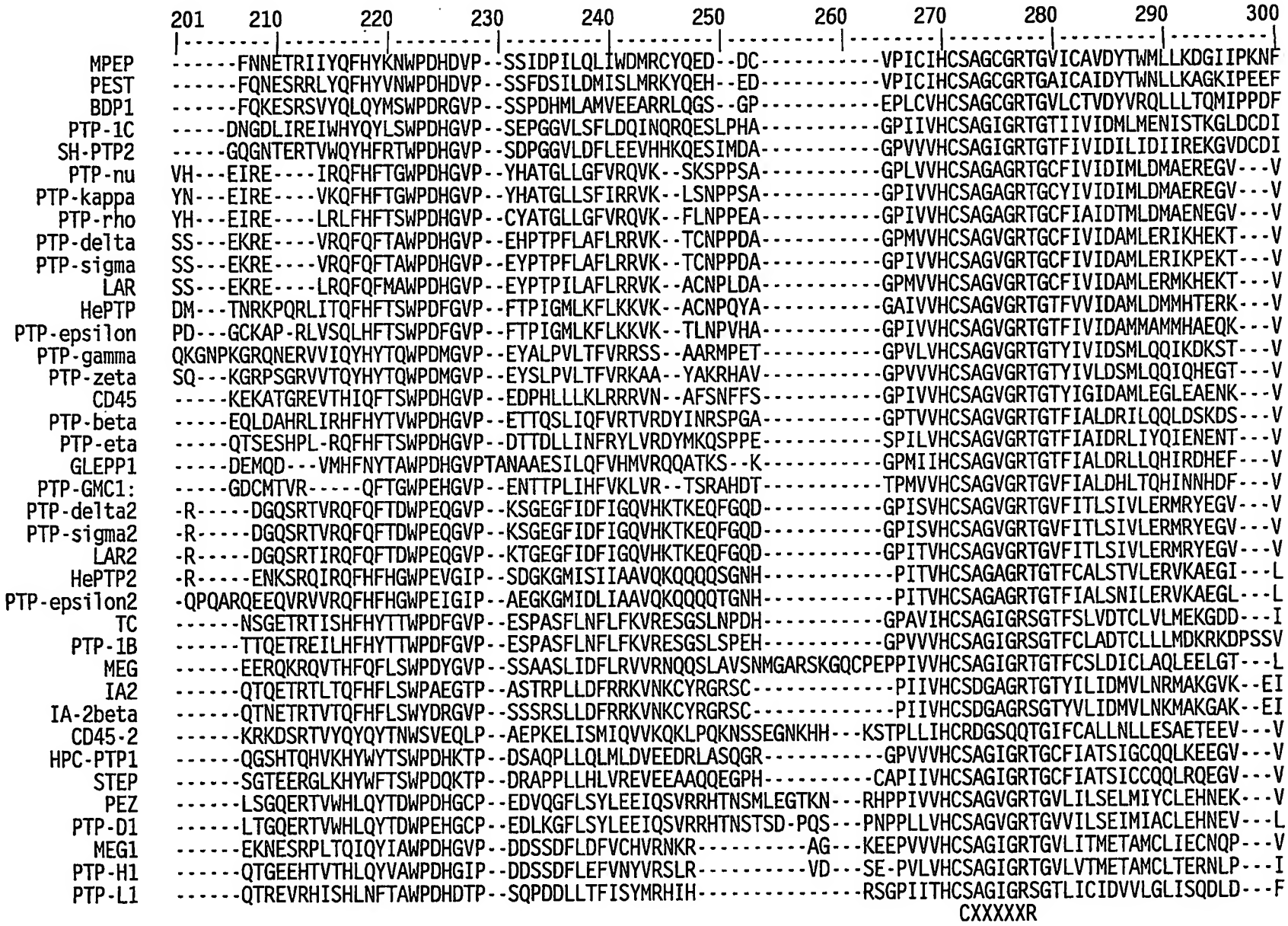
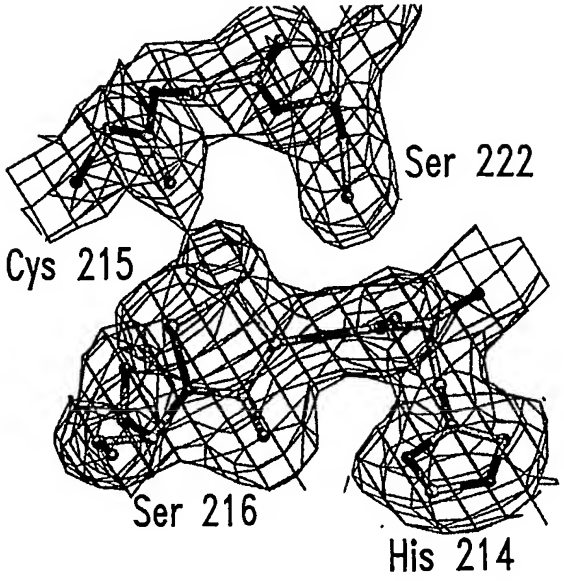


FIG. 6

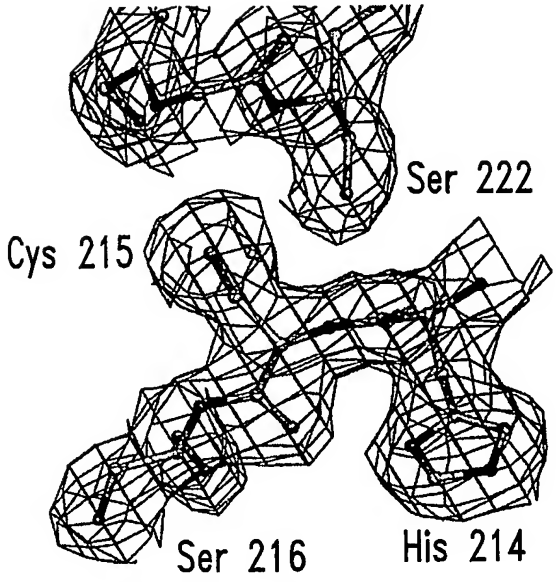
MKP-1	GGRVFVHCQAGISRSATIC-LAYLM
MKP-2,4	RGRVLVHCQAGISRSATIC-LAYLM
PYST1	NCGVLVHCLAGISRSVTVT-VAYLM
MKP-4	NCGVLVHCLAGVSRSVTVT-VAYLM
MKP-5	GGKVLVHCEAGISRSPTIC-MAYLM
MKP-7	NGCVLVHCLAGISRSATIA-IAYIM
PYST-2	KCGVLVHCLAGISRSVTVT-VAYLM
PAC1	GGRVLVHCQAGISRSATIC-LAYLI
hVH-5	SCQVIVHCLAGISRSATIA-IAYIM
EPM2	GHIVYVHCNAGVGRSTAAV-CGWLQ
VHR	NGRVLVHCREGYSRSPTLV-IAYLM
STYXb	GEKVLVHGNAGISRSAAFV-IAYIM
STYX-2	GSVILIFSTQGISRSCAAI-IAYLM
STYX-3	SGKVLVSSEMGISRSAVLV-VAYLM
WO01/64911	GGACLVYCKNGRSRSAAVC-TAYLM
MKP- Consensus 1:	NGRVLVHCQAGISRSGTNI-LAYLM
PTEN	NHVAAIHCKAGKGRTGVMI-CAYLL
TPTE	ENIVAIHCKGGTDRTGTMV-CAFLI
TPIP-alpha	ENIVAIHCKGGKGRTGTMV-CALLI
XM_085008	ENIVVIHCKGGKGRTGTMV-CACLI
AL137707	ENIVVIHCKGGKGRTGTMV-CACLI
KAP	YRKTLIHCYGGLGRSCLVA-ACLLL
MTM1 (PIP3 substrate)	KSSVLVHCSDGWDRTAQLTSLAMLM
MTMR3	QRPVLVHCSDGWDRTPQIVALAKLL
PRL-1	GCCVAVHCVAGLGRAPVLVALA-LI
Hpr13	GSCVAVHCVAGLGRAPVLVALA-LI
PIR1	DKLIGVHCTHGLNRTGYLI-CRYLI
HsGAK	HKNCVVHCMDGRAASAVAV-CSFLC
ACP-1	TKSVLFVCLGNICRSPIAEAVFRKL
CDC14B	EGAIAVHCKAGLGRTGTLI-ACYIM
CDC25B	RVILIFHCEFSSERGPRMCRFIRER
AC004099 - DSP- 1	HGATLVHCAAGVSRSATLC-IAYLM
AA915932 - DSP- 2	QGRTLLHCAAGVSRSAALC-LAYLM
AA374753 - DSP- 3	GESCLVHCLAGVSRSVTLV-IAYIM
AI031656 - DSP- 4	DGVVLVHCNAGVSRAAAIV-IGFLM
AA314946 - DSP- 5	GRSVLVHCHAGVSRSVAII-TAFLM
AI208559 - DSP- 6	GKCVYVHCKAGRSRSATMV-AAYLI
AA602372 - DSP- 7	TGRVLVHCAMGVSRSATLV-LAFLM
AI025489 - DSP- 8	QGLTLLHCMAGVSRSASLC-LAYLM
AI372800 - DSP- 9	GGKILVHCAVGVSRSATLV-LAYLM
N70334 - DSP-10	GKGLLIHCQAGVSRSATIV-IAYLM
AA479435 - DSP-11	GEAVGVHCALGFGRTGTML-ACYLV
AC008081 - DSP-12	HSKCLVHCKMGVSRSASTV-IAYAM
AC010189 - DSP-13	GSKCLVHCKMGVSRSASTV-IAYAM
AC018511 - DSP-14	HSKILVHCVMGRSRSATLV-LAYLM
AK001790 - DSP-15	GTHVLVHCKMGVSRSAATV-LAYAM
AC007619 - DSP-16	NGCVLVHCLAGISRSATIA-IAYIM
AL392111 - DSP-17	GAKVLVHCVVGVSRSATLV-LAYLM
BF377364 - PTP-SN	GGNCLVHCFAGISRSTTIV-TAYVM
CONSENSUS MOTIF	-CXXXXXR-

FIG. 7



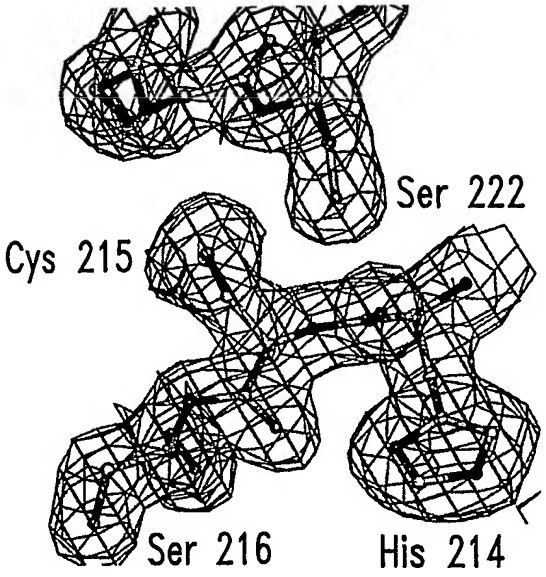
Sulfenyl-amide (SN)

FIG. 8A



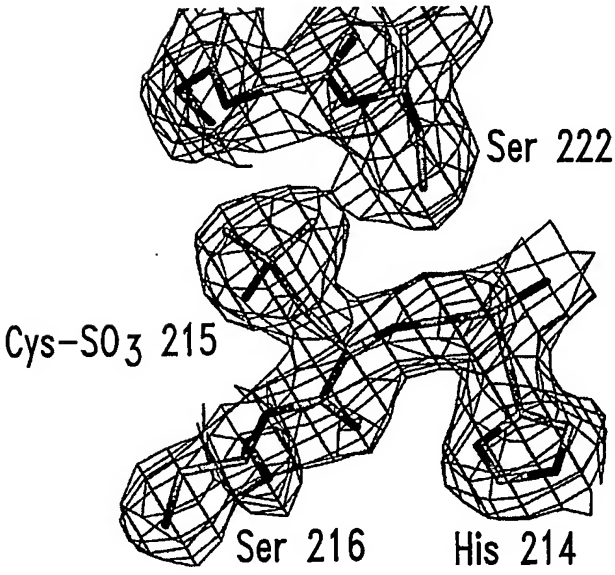
SN after DTT reduction

FIG. 8B



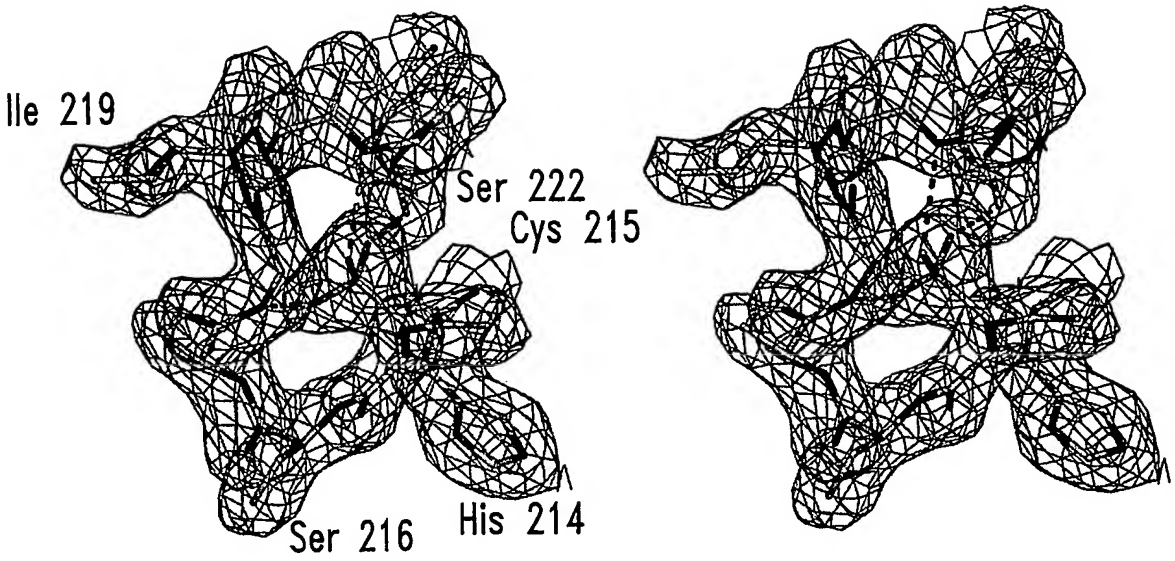
SN after glutathione reduction

FIG. 8C



SN oxidized to SO_3 after 3 months

FIG. 8D



PTP1B–SO3 stereo–view of the PTP loop of PTP1B incubated in pervanadate

FIG. 8E

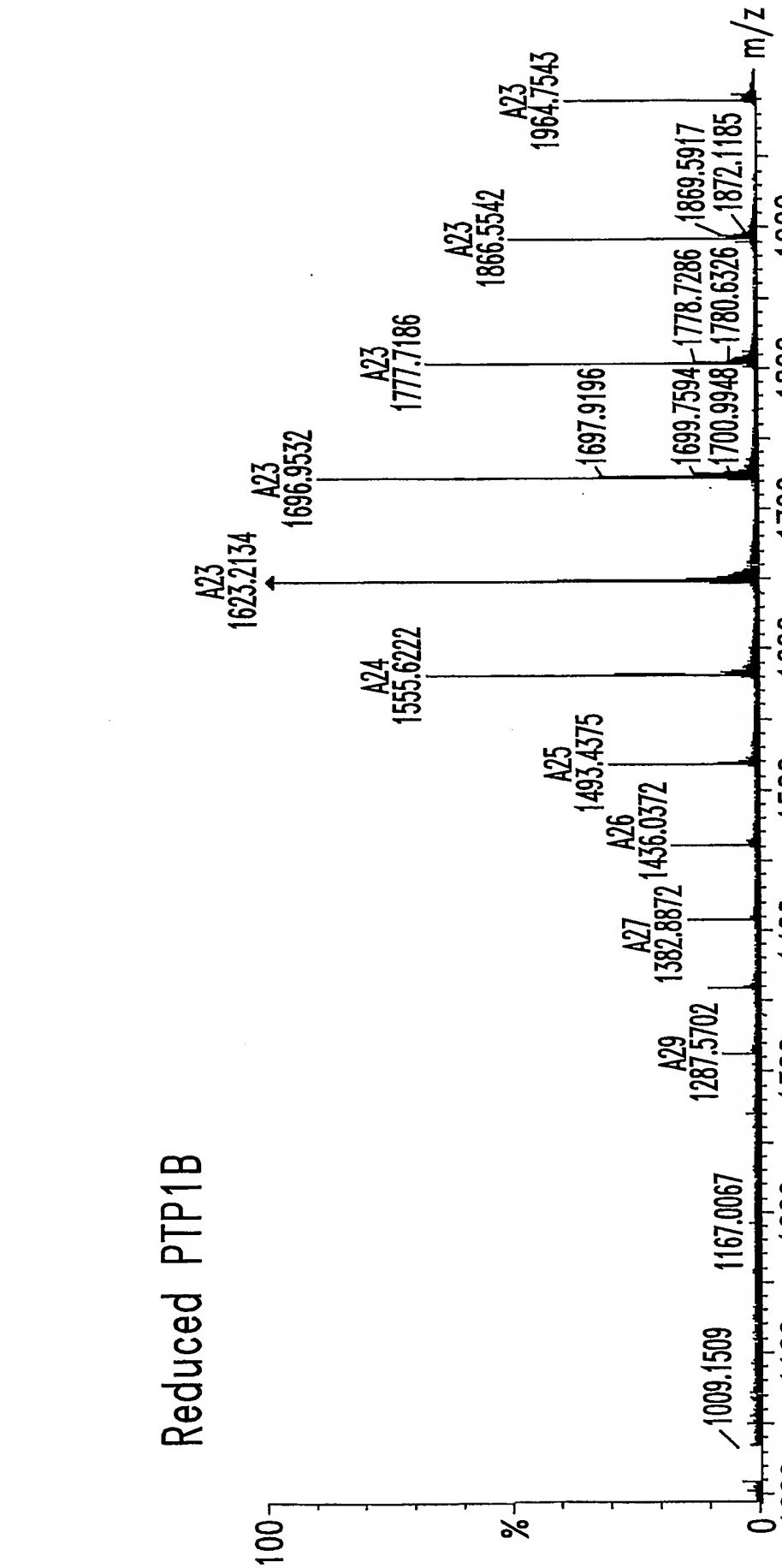

Reduced PTP1B
100
%
0
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
m/z
1009.1509
1167.0067
A29
1287.5702
A27
1382.8872
A26
1436.0372
A25
1493.4375
A24
1555.6222
A23
1623.2134
A23
1696.9532
1697.9196
1699.7594
1700.9948
A23
1777.7186
1778.7286
1780.6326
A23
1866.5542
1869.5917
1872.1185
A23
1964.7543

FIG. 9A

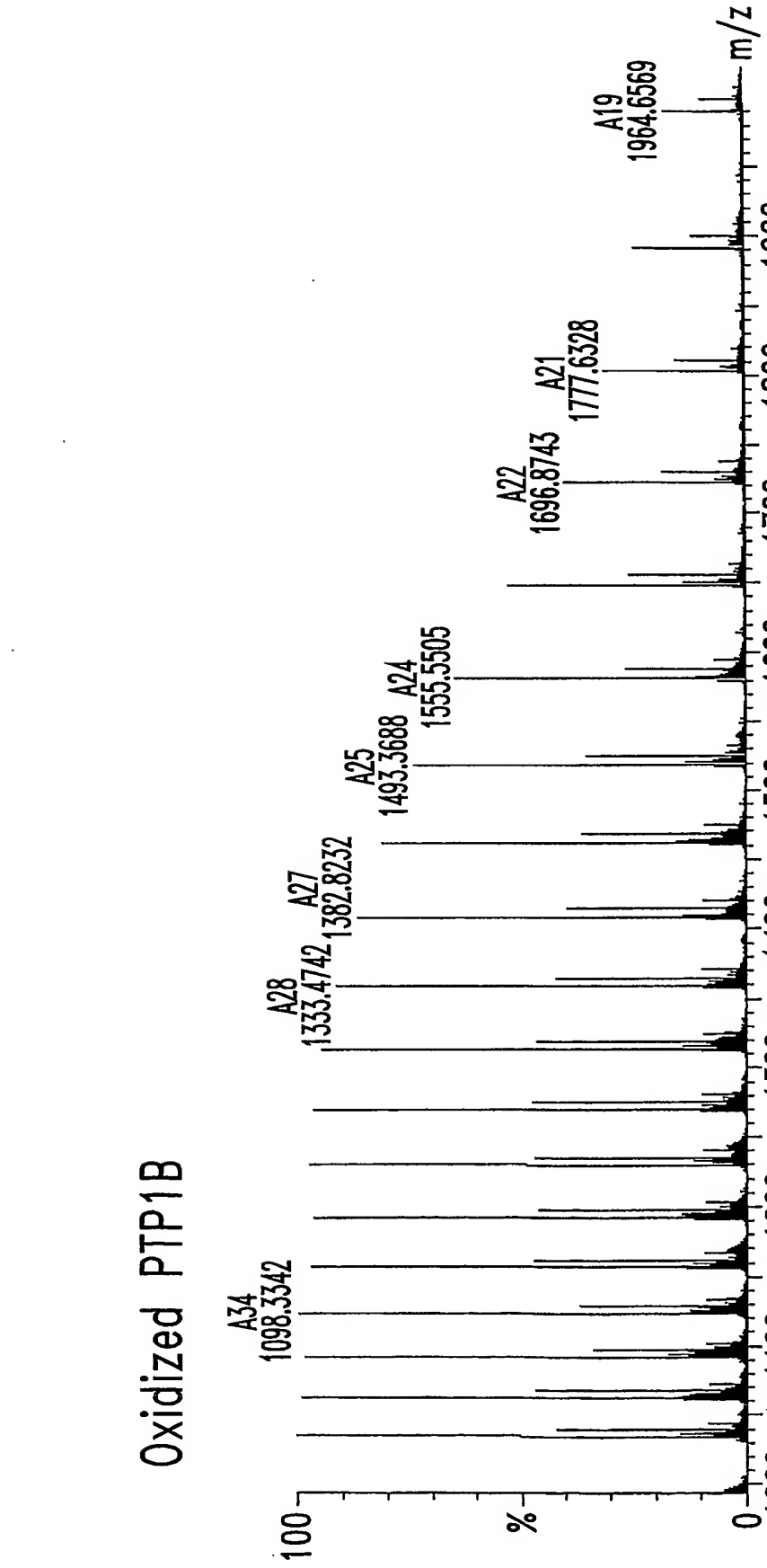

Oxidized PTP1B
A34
1098.3342
A28
1333.4742
A27
1382.8232
A25
1493.3688
A24
1555.5505
A22
1696.8743
A21
1777.6328
A19
1964.6569
m/z
100
%
0
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900

FIG. 9B

SEQUENCE LISTING

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Barford, David
Neel, Benjamin G.
Flint, Andrew J.

<120> NOVEL FORM OF PROTEIN TYROSINE PHOSPHATASES AND METHODS FOR IDENTIFYING MOLECULES BINDING THERETO

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<213> UNKNOWN

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<223> Xaa = Any Amino Acid

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1 5

<210> 4
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<223> Xaa = Any Amino Acid

<400> 4
Ile His Cys Xaa Xaa Xaa Xaa Xaa Arg
1 5

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<221> VARIANT
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<212> DNA
<213> Homo sapiens

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<212> PRT

<213> Homo sapiens

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Arg Val Ala Lys Leu Pro Lys Asn Lys Asn Arg Asn Arg Tyr Arg Asp
        35                  40                  45
Val Ser Pro Phe Asp His Ser Arg Ile Lys Leu His Gln Glu Asp Asn
    50                  55                  60
Asp Tyr Ile Asn Ala Ser Leu Ile Lys Met Glu Glu Ala Gln Arg Ser
65                  70                  75                  80
Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Gly His Phe Trp
                85                  90                  95
Glu Met Val Trp Glu Gln Lys Ser Arg Gly Val Val Met Leu Asn Arg
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Val Met Glu Lys Gly Ser Leu Lys Cys Ala Gln Tyr Trp Pro Gln Lys
        115                 120                 125
Glu Glu Lys Glu Met Ile Phe Glu Asp Thr Asn Leu Lys Leu Thr Leu
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Ile Ser Glu Asp Ile Lys Ser Tyr Tyr Thr Val Arg Gln Leu Glu Leu
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Glu Asn Leu Thr Thr Gln Glu Thr Arg Glu Ile Leu His Phe His Tyr
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Thr Thr Trp Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe Leu
            180                 185                 190
Asn Phe Leu Phe Lys Val Arg Glu Ser Gly Ser Leu Ser Pro Glu His
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Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly Arg Ser Gly Thr
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Phe Cys Leu Ala Asp Thr Cys Leu Leu Leu Met Asp Lys Arg Lys Asp
225                 230                 235                 240
Pro Ser Ser Val Asp Ile Lys Lys Val Leu Leu Glu Met Arg Lys Phe
                245                 250                 255
Arg Met Gly Leu Ile Gln Thr Ala Asp Gln Leu Arg Phe Ser Tyr Leu
            260                 265                 270
Ala Val Ile Glu Gly Ala Lys Phe Ile Met Gly Asp Ser Ser Val Gln
        275                 280                 285
Asp Gln Trp Lys Glu Leu Ser His Glu Asp Leu Glu Pro Pro Pro Glu
    290                 295                 300
His Ile Pro Pro Pro Pro Arg Pro Pro Lys Arg Ile Leu Glu Pro His
305                 310                 315                 320
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Glu Thr Gln Glu Asp Lys Asp Cys Pro Ile Lys Glu Glu Lys Gly Ser
            340                 345                 350
Pro Leu Asn Ala Ala Pro Tyr Gly Ile Glu Ser Met Ser Gln Asp Thr
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Glu Val Arg Ser Arg Val Val Gly Gly Ser Leu Arg Gly Ala Gln Ala
    370                 375                 380
Ala Ser Pro Ala Lys Gly Glu Pro Ser Leu Pro Glu Lys Asp Glu Asp
385                 390                 395                 400
His Ala Leu Ser Tyr Trp Lys Pro Phe Leu Val Asn Met Cys Val Ala
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<213> Homo sapiens

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35 40 45
Val Ser Pro Phe Asp His Ser Arg Ile Lys Leu His Gln Glu Asp Asn
50 55 60
Asp Tyr Ile Asn Ala Ser Leu Ile Lys Met Glu Glu Ala Gln Arg Ser
65 70 75 80
Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Gly His Phe Trp
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100 105 110
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115 120 125
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Asp Tyr Ile Asn Ala Ser Leu Ile Lys Met Glu Glu Ala Gln Arg Ser
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Gln Ser Ser Ala Met His Ser Val Ser Ser Met Ser Pro Asp Thr Glu
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Val Arg Arg Arg Met Val Gly Gly Gly Leu Gln Ser Ala Gln Ala Ser
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Ser Gly Pro Lys Lys Tyr Phe Pro Ile Pro Val Glu His Leu Glu Glu
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Phe Asn Ser Leu Pro Ser Gly His Ile Gln Gly Thr Phe Glu Leu Ala
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Asn Lys Glu Glu Asn Arg Glu Lys Asn Arg Tyr Pro Asn Ile Leu Pro
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Asn Asp His Ser Arg Val Ile Leu Ser Gln Leu Asp Gly Ile Pro Cys
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Ser Asp Tyr Ile Asn Ala Ser Tyr Ile Asp Gly Tyr Lys Glu Lys Asn
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Lys Phe Ile Ala Ala Gln Gly Pro Lys Gln Glu Thr Val Asn Asp Phe
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Trp Arg Met Val Trp Glu Gln Lys Ser Ala Thr Ile Val Met Leu Thr
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Asn Leu Lys Glu Arg Lys Glu Glu Lys Cys His Gln Tyr Trp Pro Asp
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Gln Gly Cys Trp Thr Tyr Gly Asn Ile Arg Val Cys Val Glu Asp Cys
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Val Val Leu Val Asp Tyr Thr Ile Arg Lys Phe Cys Ile Gln Pro Gln
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Thr Ser Trp Pro Asp Phe Gly Val Pro Phe Thr Pro Ile Gly Met Leu
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Lys Phe Leu Lys Lys Val Lys Thr Leu Asn Pro Val His Ala Gly Pro
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Ile Val Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Phe Ile
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Val Phe Glu Phe Val Ser Arg Ile Arg Asn Gln Arg Pro Gln Met Val
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Gln Thr Asp Met Gln Tyr Thr Phe Ile Tyr Gln Ala Leu Leu Glu Tyr
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Leu Gln Thr Met His Gly Thr Thr Thr His Phe Asp Lys Ile Gly Leu
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Met Arg Thr Gly Asn Leu Pro Ala Asn Met Lys Lys Ala Arg Val Ile
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Gln Ile Ile Pro Tyr Asp Phe Asn Arg Val Ile Leu Ser Met Lys Arg
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Arg Gln Lys Asp Tyr Phe Ile Ala Thr Gln Gly Pro Leu Ala His Thr
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Val Glu Asp Phe Trp Arg Met Ile Trp Glu Trp Lys Ser His Thr Ile
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Val Met Leu Thr Glu Val Gln Glu Arg Glu Gln Asp Lys Cys Tyr Gln
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Tyr Trp Pro Thr Glu Gly Ser Val Thr His Gly Glu Ile Thr Ile Glu
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Val Thr Leu Asn Gln Pro Gln Ala Arg Gln Glu Glu Gln Val Arg Val
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Val Arg Gln Phe His Phe His Gly Trp Pro Glu Ile Gly Ile Pro Ala
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Glu Gly Lys Gly Met Ile Asp Leu Ile Ala Ala Val Gln Lys Gln Gln
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Gly Arg Thr Gly Thr Phe Ile Ala Leu Ser Asn Ile Leu Glu Arg Val
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Thr Asn Thr Ser Glu Asp Gly Glu Ser Ser Gly Ala Asn Asp Ser Leu
                85                  90                  95
Arg Thr Pro Glu Gln Gly Ser Asn Gly Thr Asp Gly Ala Ser Gln Lys
            100                 105                 110
Thr Pro Ser Ser Thr Gly Pro Ser Pro Val Phe Asp Ile Lys Ala Val
        115                 120                 125
Ser Ile Ser Pro Thr Asn Val Ile Leu Thr Trp Lys Ser Asn Asp Thr
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Ala Ala Ser Glu Tyr Lys Tyr Val Val Lys His Lys Met Glu Asn Glu
145                 150                 155                 160
Lys Thr Ile Thr Val Val His Gln Pro Trp Cys Asn Ile Thr Gly Leu
                165                 170                 175
Arg Pro Ala Thr Ser Tyr Val Phe Ser Ile Thr Pro Gly Ile Gly Asn
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Glu Thr Trp Gly Asp Pro Arg Val Ile Lys Val Ile Thr Glu Pro Ile
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Pro Val Ser Asp Leu Arg Val Ala Leu Thr Gly Val Arg Lys Ala Ala
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Leu Ser Trp Ser Asn Gly Asn Gly Thr Ala Ser Cys Arg Val Leu Leu
225                 230                 235                 240
Glu Ser Ile Gly Ser His Glu Glu Leu Thr Gln Asp Ser Arg Leu Gln
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Val Asn Ile Ser Asp Leu Lys Pro Gly Val Gln Tyr Asn Ile Asn Pro
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Tyr Leu Leu Gln Ser Asn Lys Thr Lys Gly Asp Pro Leu Gly Thr Glu
        275                 280                 285
Gly Gly Leu Asp Ala Ser Asn Thr Glu Arg Ser Arg Ala Gly Ser Pro
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Thr Ala Pro Val His Asp Glu Ser Leu Val Gly Pro Val Asp Pro Ser
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Ser Gly Gln Gln Ser Arg Asp Thr Glu Val Leu Leu Val Gly Leu Glu
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Pro Gly Thr Arg Tyr Asn Ala Thr Val Tyr Ser Gln Ala Ala Asn Gly
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Thr Glu Gly Gln Pro Gln Ala Ile Glu Phe Arg Thr Asn Ala Ile Gln
        355                 360                 365
Val Phe Asp Val Thr Ala Val Asn Ile Ser Ala Thr Ser Leu Thr Leu
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Ile Trp Lys Val Ser Asp Asn Glu Ser Ser Ser Asn Tyr Thr Tyr Lys
385                 390                 395                 400
Ile His Val Ala Gly Glu Thr Asp Ser Ser Asn Leu Asn Val Ser Glu
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Pro Arg Ala Val Ile Pro Gly Leu Arg Ser Ser Thr Phe Tyr Asn Ile
            420                 425                 430
Thr Val Cys Pro Val Leu Gly Asp Ile Glu Gly Thr Pro Gly Phe Leu
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Gln Val His Thr Pro Pro Val Pro Val Ser Asp Phe Arg Val Thr Val
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Val Ser Thr Thr Glu Ile Gly Leu Ala Trp Ser Ser His Asp Ala Glu
465                 470                 475                 480
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Glu Ile Thr Thr Asn Gln Ser Ile Ile Ile Gly Gly Leu Phe Pro Gly
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Lys Ser Pro Asp Gly Ala Ser Glu Tyr Val Tyr His Leu Val Ile Glu
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Ser Lys His Gly Ser Asn His Thr Ser Thr Tyr Asp Lys Ala Ile Thr
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Glu Val Asp His Val Trp Gly Asp Pro Asn Ser Thr Ala Gln Tyr Thr
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625                 630                 635                 640
Ala Thr Leu Ser Trp Gln Asn Phe Asp Asp Ala Ser Pro Thr Tyr Ser
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Tyr Cys Leu Leu Ile Glu Lys Ala Gly Asn Ser Ser Asn Ala Thr Gln
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Val Val Thr Asp Ile Gly Ile Thr Asp Ala Thr Val Thr Glu Leu Ile
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Pro Gly Ser Ser Tyr Thr Val Glu Ile Phe Ala Gln Val Gly Asp Gly
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Ser Met Ala Ser Phe Asp Cys Glu Val Val Pro Lys Glu Pro Ala Leu
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Val Leu Lys Trp Thr Cys Pro Pro Gly Ala Asn Ala Gly Phe Glu Leu
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Ser Ser Glu Asn Gly Thr Glu Tyr Arg Thr Glu Val Thr Tyr Leu Asn
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Pro Pro Pro Asp Gly Ser Pro Asn Ile Thr Ser Val Ser His Asn Ser
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Val Lys Val Lys Phe Ser Gly Phe Glu Ala Ser His Gly Pro Ile Lys
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ccagcaatgt gtccaacatt gatgtaagta ccaacaccac agcagcaact ttaagttggc 2280
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cgggcacttt cattgccatt gatcgtctca tctaccagat agagaatgag aacaccgtgg 4140
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<210> 40
<211> 1337
<212> PRT
<213> Homo sapiens

<400> 40
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Leu Arg Trp Ala Leu Pro Leu Leu Leu Leu Leu Leu Arg Leu Gly Gln
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Ile Leu Cys Ala Gly Gly Thr Pro Ser Pro Ile Pro Asp Pro Ser Val
35 40 45
Ala Thr Val Ala Thr Gly Glu Asn Gly Ile Thr Gln Ile Ser Ser Thr
50 55 60
Ala Glu Ser Phe His Lys Gln Asn Gly Thr Gly Thr Pro Gln Val Glu
65 70 75 80
Thr Asn Thr Ser Glu Asp Gly Glu Ser Ser Gly Ala Asn Asp Ser Leu
85 90 95
Arg Thr Pro Glu Gln Gly Ser Asn Gly Thr Asp Gly Ala Ser Gln Lys
100 105 110
Thr Pro Ser Ser Thr Gly Pro Ser Pro Val Phe Asp Ile Lys Ala Val
115 120 125
Ser Ile Ser Pro Thr Asn Val Ile Leu Thr Trp Lys Ser Asn Asp Thr
130 135 140
Ala Ala Ser Glu Tyr Lys Tyr Val Val Lys His Lys Met Glu Asn Glu
145 150 155 160
Lys Thr Ile Thr Val Val His Gln Pro Trp Cys Asn Ile Thr Gly Leu
165 170 175
Arg Pro Ala Thr Ser Tyr Val Phe Ser Ile Thr Pro Gly Ile Gly Asn
180 185 190
Glu Thr Trp Gly Asp Pro Arg Val Ile Lys Val Ile Thr Glu Pro Ile
195 200 205
Pro Val Ser Asp Leu Arg Val Ala Leu Thr Gly Val Arg Lys Ala Ala
210 215 220
Leu Ser Trp Ser Asn Gly Asn Gly Thr Ala Ser Cys Arg Val Leu Leu
225 230 235 240
Glu Ser Ile Gly Ser His Glu Glu Leu Thr Gln Asp Ser Arg Leu Gln
245 250 255

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Val Asn Ile Ser Gly Leu Lys Pro Gly Val Gln Tyr Asn Ile Asn Pro
            260                 265                 270
Tyr Leu Leu Gln Ser Asn Lys Thr Lys Gly Asp Pro Leu Gly Thr Glu
        275                 280                 285
Gly Gly Leu Asp Ala Ser Asn Thr Glu Arg Ser Arg Ala Gly Ser Pro
    290                 295                 300
Thr Ala Pro Val His Asp Glu Ser Leu Val Gly Pro Val Asp Pro Ser
305                 310                 315                 320
Ser Gly Gln Gln Ser Arg Asp Thr Glu Val Leu Leu Val Gly Leu Glu
                325                 330                 335
Pro Gly Thr Arg Tyr Asn Ala Thr Val Tyr Ser Gln Ala Ala Asn Gly
            340                 345                 350
Thr Glu Gly Gln Pro Gln Ala Ile Glu Phe Arg Thr Asn Ala Ile Gln
        355                 360                 365
Val Phe Asp Val Thr Ala Val Asn Ile Ser Ala Thr Ser Leu Thr Leu
    370                 375                 380
Ile Trp Lys Val Ser Asp Asn Glu Ser Ser Ser Asn Tyr Thr Tyr Lys
385                 390                 395                 400
Ile His Val Ala Gly Glu Thr Asp Ser Ser Asn Leu Asn Val Ser Glu
                405                 410                 415
Pro Arg Ala Val Ile Pro Gly Leu Arg Ser Ser Thr Phe Tyr Asn Ile
            420                 425                 430
Thr Val Cys Pro Val Leu Gly Asp Ile Glu Gly Thr Pro Gly Phe Leu
        435                 440                 445
Gln Val His Thr Pro Pro Val Pro Val Ser Asp Phe Arg Val Thr Val
    450                 455                 460
Val Ser Thr Thr Glu Ile Gly Leu Ala Trp Ser Ser His Asp Ala Glu
465                 470                 475                 480
Ser Phe Gln Met His Ile Thr Gln Glu Gly Ala Gly Asn Ser Arg Val
                485                 490                 495
Glu Ile Thr Thr Asn Gln Ser Ile Ile Ile Gly Gly Leu Phe Pro Gly
            500                 505                 510
Thr Lys Tyr Cys Phe Glu Ile Val Pro Lys Gly Pro Asn Gly Thr Glu
        515                 520                 525
Gly Ala Ser Arg Thr Val Cys Asn Arg Thr Val Pro Ser Ala Val Phe
    530                 535                 540
Asp Ile His Val Val Tyr Val Thr Thr Thr Glu Met Trp Leu Asp Trp
545                 550                 555                 560
Lys Ser Pro Asp Gly Ala Ser Glu Tyr Val Tyr His Leu Val Ile Glu
                565                 570                 575
Ser Lys His Gly Ser Asn His Thr Ser Thr Tyr Asp Lys Ala Ile Thr
            580                 585                 590
Leu Gln Gly Leu Ile Pro Gly Thr Leu Tyr Asn Ile Thr Ile Ser Pro
        595                 600                 605
Glu Val Asp His Val Trp Gly Asp Pro Asn Ser Thr Ala Gln Tyr Thr
    610                 615                 620
Arg Pro Ser Asn Val Ser Asn Ile Asp Val Ser Thr Asn Thr Thr Ala
625                 630                 635                 640
Ala Thr Leu Ser Trp Gln Asn Phe Asp Asp Ala Ser Pro Thr Tyr Ser
                645                 650                 655
Tyr Cys Leu Leu Ile Glu Lys Ala Gly Asn Ser Ser Asn Ala Thr Gln
            660                 665                 670
Val Val Thr Asp Ile Gly Ile Thr Asp Ala Thr Val Thr Glu Leu Ile
        675                 680                 685
Pro Gly Ser Ser Tyr Thr Val Glu Ile Phe Ala Gln Val Gly Asp Gly
    690                 695                 700
Ile Lys Ser Leu Glu Pro Gly Arg Lys Ser Phe Cys Thr Asp Pro Ala
705                 710                 715                 720
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Ser Met Ala Ser Phe Asp Cys Glu Val Val Pro Lys Glu Pro Ala Leu
                725                 730                 735
Val Leu Lys Trp Thr Cys Pro Pro Gly Ala Asn Ala Gly Phe Glu Leu
            740                 745                 750
Glu Val Ser Ser Gly Ala Trp Asn Asn Ala Thr His Leu Glu Ser Cys
        755                 760                 765
Ser Ser Glu Asn Gly Thr Glu Tyr Arg Thr Glu Val Thr Tyr Leu Asn
    770                 775                 780
Phe Ser Thr Ser Tyr Asn Ile Ser Ile Thr Thr Val Ser Cys Gly Lys
785                 790                 795                 800
Met Ala Ala Pro Thr Arg Asn Thr Cys Thr Thr Gly Ile Thr Asp Pro
                805                 810                 815
Pro Pro Pro Asp Gly Ser Pro Asn Ile Thr Ser Val Ser His Asn Ser
            820                 825                 830
Val Lys Val Lys Phe Ser Gly Phe Glu Ala Ser His Gly Pro Ile Lys
        835                 840                 845
Ala Tyr Ala Val Ile Leu Thr Thr Gly Glu Ala Gly His Pro Ser Ala
    850                 855                 860
Asp Val Leu Lys Tyr Thr Tyr Asp Asp Phe Lys Lys Gly Ala Ser Asp
865                 870                 875                 880
Thr Tyr Val Thr Tyr Leu Ile Arg Thr Glu Glu Lys Gly Arg Ser Gln
                885                 890                 895
Ser Leu Ser Glu Val Leu Lys Tyr Glu Ile Asp Val Gly Asn Glu Ser
            900                 905                 910
Thr Thr Leu Gly Tyr Leu Gln Trp Glu Ala Gly Thr Ser Gly Leu Leu
        915                 920                 925
Pro Ala Cys Val Ala Gly Phe Thr Asn Ile Thr Phe His Pro Gln Asn
    930                 935                 940
Lys Gly Leu Ile Asp Gly Ala Glu Ser Tyr Val Ser Phe Ser Arg Tyr
945                 950                 955                 960
Ser Asp Ala Val Ser Leu Pro Gln Asp Pro Gly Val Ile Cys Gly Ala
                965                 970                 975
Val Phe Gly Cys Ile Phe Gly Ala Leu Val Ile Val Thr Val Gly Gly
            980                 985                 990
Phe Ile Phe Trp Arg Lys Lys Arg Lys Asp Ala Lys Asn Asn Glu Val
        995                 1000                1005
Ser Phe Ser Gln Ile Lys Pro Lys Lys Ser Lys Leu Ile Arg Val Glu
    1010                1015                1020
Asn Phe Glu Ala Tyr Phe Lys Lys Gln Gln Ala Asp Ser Asn Cys Gly
1025                1030                1035                1040
Phe Ala Glu Glu Tyr Glu Asp Leu Lys Leu Val Gly Ile Ser Gln Pro
                1045                1050                1055
Lys Tyr Ala Ala Glu Leu Ala Glu Asn Arg Gly Lys Asn Arg Tyr Asn
            1060                1065                1070
Asn Val Leu Pro Tyr Asp Ile Ser Arg Val Lys Leu Ser Val Gln Thr
        1075                1080                1085
His Ser Thr Asp Asp Tyr Ile Asn Ala Asn Tyr Met Pro Gly Tyr His
    1090                1095                1100
Ser Lys Lys Asp Phe Ile Ala Thr Gln Gly Pro Leu Pro Asn Thr Leu
1105                1110                1115                1120
Lys Asp Phe Trp Arg Met Val Trp Glu Lys Asn Val Tyr Ala Ile Ile
                1125                1130                1135
Met Leu Thr Lys Cys Val Glu Gln Gly Arg Thr Lys Cys Glu Glu Tyr
            1140                1145                1150
Trp Pro Ser Lys Gln Ala Gln Asp Tyr Gly Asp Ile Thr Val Ala Met
        1155                1160                1165
Thr Ser Glu Ile Val Leu Pro Glu Trp Thr Ile Arg Asp Phe Thr Val
    1170                1175                1180
```

```
Lys Asn Ile Gln Thr Ser Glu Ser His Pro Leu Arg Gln Phe His Phe
1185                1190                1195                1200
Thr Ser Trp Pro Asp His Gly Val Pro Asp Thr Thr Asp Leu Leu Ile
                1205                1210                1215
Asn Phe Arg Tyr Leu Val Arg Asp Tyr Met Lys Gln Ser Pro Pro Glu
            1220                1225                1230
Ser Pro Ile Leu Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr
        1235                1240                1245
Phe Ile Ala Ile Asp Arg Leu Ile Tyr Gln Ile Glu Asn Glu Asn Thr
    1250                1255                1260
Val Asp Val Tyr Gly Ile Val Tyr Asp Leu Arg Met His Arg Pro Leu
1265                1270                1275                1280
Met Val Gln Thr Glu Asp Gln Tyr Val Phe Leu Asn Gln Cys Val Leu
                1285                1290                1295
Asp Ile Val Arg Ser Gln Lys Asp Ser Lys Val Asp Leu Ile Tyr Gln
            1300                1305                1310
Asn Thr Thr Ala Met Thr Ile Tyr Glu Asn Leu Ala Pro Val Thr Thr
        1315                1320                1325
Phe Gly Lys Thr Asn Gly Tyr Ile Ala
    1330                1335
```

<210> 41
<211> 122
<212> PRT
<213> Homo sapiens

<400> 41

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Trp Arg Met Val Trp Glu Gln Asn Val Tyr Ala Ile Ile Met Leu Thr
 1               5                  10                  15
Lys Cys Val Glu Gln Gly Arg Thr Lys Cys Glu Glu Tyr Trp Pro Ser
            20                  25                  30
Lys Gln Ala Gln Asp Tyr Gly Asp Ile Thr Val Ala Met Thr Ser Glu
        35                  40                  45
Ile Val Leu Pro Glu Trp Thr Ile Arg Asp Phe Thr Val Lys Asn Ile
    50                  55                  60
Gln Thr Ser Glu Ser His Pro Leu Arg Gln Phe His Phe Thr Ser Trp
65                  70                  75                  80
Pro Asp His Gly Val Pro Asp Thr Thr Asp Leu Leu Ile Asn Phe Arg
                85                  90                  95
Tyr Leu Val Arg Asp Tyr Met Lys Gln Ser Pro Pro Glu Ser Glu Ile
            100                 105                 110
Leu Val His Cys Ser Ala Gly Ile Gly Arg
        115                 120
```

<210> 42
<211> 2543
<212> DNA
<213> Homo sapiens

<400> 42

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cggccccagg cctggagggg ggtctgtgcg cggccggctg gctctgcccc gcgtccggtc 60
ccgagcgggc ctccctcggg ccagcccgat gtgaccgagc ccagcggagc ctgagcaagg 120
agcgggtccg tcgcggagcc ggagggcggg aggaacatga catcgcggag atggtttcac 180
ccaaatatca ctggtgtgga ggcagaaaac ctactgttga caagaggagt tgatggcagt 240
tttttggcaa ggcctagtaa aagtaaccct ggagacttca cactttccgt tagaagaaat 300
ggagctgtca cccacatcaa gattcagaac actggtgatt actatgacct gtatggaggg 360
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gagaaatttg ccactttggc tgagttggtc cagtattaca tggaacatca cgggcaatta 420
aaagagaaga atggagatgt cattgagctt aaatatcctc tgaactgtgc agatcctacc 480
tctgaaaggt ggtttcatgg acatctctct gggaaagaag cagagaaatt attaactgaa 540
aaaggaaaac atggtagttt tcttgtacga gagagccaga gccaccctgg agattttgtt 600
ctttctgtgc gcactggtga tgacaaaggg gagagcaatg acggcaagtc taaagtgacc 660
catgttatga ttcgctgtca ggaactgaaa tacgacgttg gtggaggaga acggtttgat 720
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agaacaatct catttaccat catgtatcca gtagtggata attcattttg atggcttcta 2460
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gcattaaaga gtcatagaaa aaa 2543

<210> 43
<211> 593
<212> PRT
<213> Homo sapiens

<400> 43
Met Thr Ser Arg Arg Trp Phe His Pro Asn Ile Thr Gly Val Glu Ala
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20 25 30
Pro Ser Lys Ser Asn Pro Gly Asp Phe Thr Leu Ser Val Arg Arg Asn
35 40 45
Gly Ala Val Thr His Ile Lys Ile Gln Asn Thr Gly Asp Tyr Tyr Asp
50 55 60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Ala Glu Leu Val Gln Tyr
65 70 75 80
Tyr Met Glu His His Gly Gln Leu Lys Glu Lys Asn Gly Asp Val Ile
85 90 95
Glu Leu Lys Tyr Pro Leu Asn Cys Ala Asp Pro Thr Ser Glu Arg Trp
100 105 110

```
Phe His Gly His Leu Ser Gly Lys Glu Ala Glu Lys Leu Leu Thr Glu
        115                 120                 125
Lys Gly Lys His Gly Ser Phe Leu Val Arg Glu Ser Gln Ser His Pro
    130                 135                 140
Gly Asp Phe Val Leu Ser Val Arg Thr Gly Asp Asp Lys Gly Glu Ser
145                 150                 155                 160
Asn Asp Gly Lys Ser Lys Val Thr His Val Met Ile Arg Cys Gln Glu
                165                 170                 175
Leu Lys Tyr Asp Val Gly Gly Gly Glu Arg Phe Asp Ser Leu Thr Asp
            180                 185                 190
Leu Val Glu His Tyr Lys Lys Asn Pro Met Val Glu Thr Leu Gly Thr
        195                 200                 205
Val Leu Gln Leu Lys Gln Pro Leu Asn Thr Thr Arg Ile Asn Ala Ala
    210                 215                 220
Glu Ile Glu Ser Arg Val Arg Glu Leu Ser Lys Leu Ala Glu Thr Thr
225                 230                 235                 240
Asp Lys Val Lys Gln Gly Phe Trp Glu Glu Phe Glu Thr Leu Gln Gln
                245                 250                 255
Gln Glu Cys Lys Leu Leu Tyr Ser Arg Lys Glu Gly Gln Arg Gln Glu
            260                 265                 270
Asn Lys Asn Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Thr
        275                 280                 285
Arg Val Val Leu His Asp Gly Asp Pro Asn Glu Pro Val Ser Asp Tyr
    290                 295                 300
Ile Asn Ala Asn Ile Ile Met Pro Glu Phe Glu Thr Lys Cys Asn Asn
305                 310                 315                 320
Ser Lys Pro Lys Lys Ser Tyr Ile Ala Thr Gln Gly Cys Leu Gln Asn
                325                 330                 335
Thr Val Asn Asp Phe Trp Arg Met Val Phe Gln Glu Asn Ser Arg Val
            340                 345                 350
Ile Val Met Thr Thr Lys Glu Val Glu Arg Gly Lys Ser Lys Cys Val
        355                 360                 365
Lys Tyr Trp Pro Asp Glu Tyr Ala Leu Lys Glu Tyr Gly Val Met Arg
    370                 375                 380
Val Arg Asn Val Lys Glu Ser Ala Ala His Asp Tyr Thr Leu Arg Glu
385                 390                 395                 400
Leu Lys Leu Ser Lys Val Gly Gln Gly Asn Thr Glu Arg Thr Val Trp
                405                 410                 415
Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val Pro Ser Asp Pro
            420                 425                 430
Gly Gly Val Leu Asp Phe Leu Glu Glu Val His His Lys Gln Glu Ser
        435                 440                 445
Ile Met Asp Ala Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly
    450                 455                 460
Arg Thr Gly Thr Phe Ile Val Ile Asp Ile Leu Ile Asp Ile Ile Arg
465                 470                 475                 480
Glu Lys Gly Val Asp Cys Asp Ile Asp Val Pro Lys Thr Ile Gln Met
                485                 490                 495
Val Arg Ser Gln Arg Ser Gly Met Val Gln Thr Glu Ala Gln Tyr Arg
            500                 505                 510
Phe Ile Tyr Met Ala Val Gln His Tyr Ile Glu Thr Leu Gln Arg Arg
        515                 520                 525
Ile Glu Glu Glu Gln Lys Arg Lys Arg Lys Gly His Glu Tyr Thr Asn
    530                 535                 540
Ile Lys Tyr Pro Leu Ala Asp Gln Thr Ser Gly Asp Gln Ser Pro Leu
545                 550                 555                 560
Pro Pro Cys Thr Pro Thr Pro Pro Cys Ala Glu Met Arg Glu Asp Ser
                565                 570                 575
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Ala Arg Val Tyr Glu Asn Val Gly Leu Met Gln Gln Gln Lys Ser Phe
580 585 590
Arg

<210> 44
<211> 2276
<212> DNA
<213> Homo sapiens

<400> 44
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cgcggagatg gtttcaccca aatatcactg gtgtggaggc agaaaaccta ctgttgacaa 180
gaggagttga tggcagtttt ttggcaaggc ctagtaaaag taaccctgga gacttcacac 240
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aacatcacgg gcaattaaaa gagaagaatg gagatgtcat tgagcttaaa tatcctctga 420
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<210> 45
<211> 593
<212> PRT
<213> Homo sapiens

<400> 45
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Pro Ser Lys Ser Asn Pro Gly Asp Phe Thr Leu Ser Val Arg Arg Asn
        35                  40                  45
Gly Ala Val Thr His Ile Lys Ile Gln Asn Thr Gly Asp Tyr Tyr Asp
    50                  55                  60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Ala Glu Leu Val Gln Tyr
65                  70                  75                  80
Tyr Met Glu His His Gly Gln Leu Lys Glu Lys Asn Gly Asp Val Ile
                85                  90                  95
Glu Leu Lys Tyr Pro Leu Asn Cys Ala Asp Pro Thr Ser Glu Arg Trp
            100                 105                 110
Phe His Gly His Leu Ser Gly Lys Glu Ala Glu Lys Leu Leu Thr Glu
        115                 120                 125
Lys Gly Lys His Gly Ser Phe Leu Val Arg Glu Ser Gln Ser His Pro
    130                 135                 140
Gly Asp Phe Val Leu Ser Val Arg Thr Gly Asp Asp Lys Gly Glu Ser
145                 150                 155                 160
Asn Asp Gly Lys Ser Lys Val Thr His Val Met Ile Arg Cys Gln Glu
                165                 170                 175
Leu Lys Tyr Asp Val Gly Gly Gly Glu Arg Phe Asp Ser Leu Thr Asp
            180                 185                 190
Leu Val Glu His Tyr Lys Lys Asn Pro Met Val Glu Thr Leu Gly Thr
        195                 200                 205
Val Leu Gln Leu Lys Gln Pro Leu Asn Thr Thr Arg Ile Asn Ala Ala
    210                 215                 220
Glu Ile Glu Ser Arg Val Arg Glu Leu Ser Lys Leu Ala Glu Thr Thr
225                 230                 235                 240
Asp Lys Val Lys Gln Gly Phe Trp Glu Glu Phe Glu Thr Leu Gln Gln
                245                 250                 255
Gln Glu Cys Lys Leu Leu Tyr Ser Arg Lys Glu Gly Gln Arg Gln Glu
            260                 265                 270
Asn Lys Asn Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Thr
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Arg Val Val Leu His Asp Gly Asp Pro Asn Glu Pro Val Ser Asp Tyr
    290                 295                 300
Ile Asn Ala Asn Ile Ile Met Pro Glu Phe Glu Thr Lys Cys Asn Asn
305                 310                 315                 320
Ser Lys Pro Lys Lys Ser Tyr Ile Ala Thr Gln Gly Cys Leu Gln Asn
                325                 330                 335
Thr Val Asn Asp Phe Trp Arg Met Val Phe Gln Glu Asn Ser Arg Val
            340                 345                 350
Ile Val Met Thr Thr Lys Glu Val Glu Arg Gly Lys Ser Lys Cys Val
        355                 360                 365
Lys Tyr Trp Pro Asp Glu Tyr Ala Leu Lys Glu Tyr Gly Val Met Arg
    370                 375                 380
Val Arg Asn Val Lys Glu Ser Ala Ala His Asp Tyr Thr Leu Arg Glu
385                 390                 395                 400
Leu Lys Leu Ser Lys Val Gly Gln Gly Asn Thr Glu Arg Thr Val Trp
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Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val Pro Ser Asp Pro
            420                 425                 430
Gly Gly Val Leu Asp Phe Leu Glu Glu Val His His Lys Gln Glu Ser
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Ile Met Asp Ala Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly
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Glu Lys Gly Val Asp Cys Asp Ile Asp Val Pro Lys Thr Ile Gln Met
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Val Arg Ser Gln Arg Ser Gly Met Val Gln Thr Glu Ala Gln Tyr Arg
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Phe Ile Tyr Met Ala Val Gln His Tyr Ile Glu Thr Leu Gln Arg Arg
        515                 520                 525
Ile Glu Glu Glu Gln Lys Ser Lys Arg Lys Gly His Glu Tyr Thr Asn
    530                 535                 540
Ile Lys Tyr Ser Leu Ala Asp Gln Thr Ser Gly Asp Gln Ser Pro Leu
545                 550                 555                 560
Pro Pro Cys Thr Pro Thr Pro Pro Cys Ala Glu Met Arg Glu Asp Ser
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<210> 46
<211> 2121
<212> DNA
<213> Homo sapiens

<400> 46

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<210> 47
<211> 593
<212> PRT
<213> Homo sapiens

<400> 47

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Pro	Ser	Lys	Ser	Asn	Pro	Gly	Asp	Phe	Thr	Leu	Ser	Val	Arg	Arg	Asn
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Gly	Ala	Val	Thr	His	Ile	Lys	Ile	Gln	Asn	Thr	Gly	Asp	Tyr	Tyr	Asp
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Tyr	Met	Glu	His	His	Gly	Gln	Leu	Lys	Glu	Lys	Asn	Gly	Asp	Val	Ile
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Leu	Val	Glu	His	Tyr	Lys	Lys	Asn	Pro	Met	Val	Glu	Thr	Leu	Gly	Thr
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Glu	Ile	Glu	Ser	Arg	Val	Arg	Glu	Leu	Ser	Lys	Leu	Ala	Glu	Thr	Thr
225					230					235					240
Asp	Lys	Val	Lys	Gln	Gly	Phe	Trp	Glu	Glu	Phe	Glu	Thr	Leu	Gln	Gln
				245					250					255	
Gln	Glu	Cys	Lys	Leu	Leu	Tyr	Ser	Arg	Lys	Glu	Gly	Gln	Arg	Gln	Glu
			260					265					270		
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		275					280					285			
Arg	Val	Val	Leu	His	Asp	Gly	Asp	Pro	Asn	Glu	Pro	Val	Ser	Asp	Tyr
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Ile	Asn	Ala	Asn	Ile	Ile	Met	Pro	Glu	Phe	Glu	Thr	Lys	Cys	Asn	Asn
305					310					315					320
Ser	Lys	Pro	Lys	Lys	Ser	Tyr	Ile	Ala	Thr	Gln	Gly	Cys	Leu	Gln	Asn
				325					330					335	
Thr	Val	Asn	Asp	Phe	Trp	Arg	Met	Val	Phe	Gln	Glu	Asn	Ser	Arg	Val
			340					345					350		
Ile	Val	Met	Thr	Thr	Lys	Glu	Val	Glu	Arg	Gly	Lys	Ser	Lys	Cys	Val
		355					360					365			
Lys	Tyr	Trp	Pro	Asp	Glu	Tyr	Ala	Leu	Lys	Glu	Tyr	Gly	Val	Met	Arg
	370					375					380				

Val Arg Asn Val Lys Glu Ser Ala Ala His Asp Tyr Thr Leu Arg Glu
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Leu Lys Leu Ser Lys Val Gly Gln Gly Asn Thr Glu Arg Thr Val Trp
405 410 415
Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val Pro Ser Asp Pro
420 425 430
Gly Gly Val Leu Asp Phe Leu Glu Glu Val His His Lys Gln Glu Ser
435 440 445
Ile Met Asp Ala Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly
450 455 460
Arg Thr Gly Thr Phe Ile Val Ile Asp Ile Leu Ile Asp Ile Ile Arg
465 470 475 480
Glu Lys Gly Val Asp Cys Asp Ile Asp Val Pro Lys Thr Ile Gln Met
485 490 495
Val Arg Ser Gln Arg Ser Gly Met Val Gln Thr Glu Ala Gln Tyr Arg
500 505 510
Phe Ile Tyr Met Ala Val Gln His Tyr Ile Glu Thr Leu Gln Arg Arg
515 520 525
Ile Glu Glu Glu Gln Lys Ser Lys Arg Lys Gly His Glu Tyr Thr Asn
530 535 540
Ile Lys Tyr Ser Leu Ala Asp Gln Thr Ser Gly Asp Gln Ser Pro Leu
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Pro Pro Cys Thr Pro Thr Pro Pro Cys Ala Glu Met Arg Glu Asp Ser
565 570 575
Ala Arg Val Tyr Glu Asn Val Gly Leu Met Gln Gln Gln Lys Ser Phe
580 585 590
Arg

<210> 48
<211> 1980
<212> DNA
<213> Homo sapiens

<400> 48
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<210> 49
<211> 584
<212> PRT
<213> Homo sapiens

<400> 49
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20 25 30
Pro Ser Lys Ser Asn Pro Gly Asp Phe Thr Leu Ser Val Arg Arg Asn
35 40 45
Gly Ala Val Thr His Ile Lys Ile Gln Asn Thr Gly Asp Tyr Tyr Asp
50 55 60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Ala Glu Leu Val Gln Tyr
65 70 75 80
Tyr Met Glu His His Gly Gln Leu Lys Glu Lys Asn Gly Asp Val Ile
85 90 95
Glu Leu Lys Tyr Pro Leu Asn Cys Ala Asp Pro Thr Ser Glu Arg Trp
100 105 110
Phe His Gly His Leu Ser Gly Lys Glu Ala Glu Lys Leu Leu Thr Glu
115 120 125
Lys Gly Lys His Gly Ser Phe Leu Val Arg Glu Ser Gln Ser His Pro
130 135 140
Gly Asp Phe Val Leu Ser Val Arg Thr Gly Asp Asp Lys Gly Glu Ser
145 150 155 160
Asn Asp Gly Lys Ser Lys Val Thr His Val Met Ile Arg Cys Gln Glu
165 170 175
Leu Lys Tyr Asp Val Gly Gly Gly Glu Arg Phe Asp Ser Leu Thr Asp
180 185 190
Leu Val Glu His Tyr Lys Lys Asn Pro Met Val Glu Thr Leu Gly Thr
195 200 205
Val Leu Gln Leu Lys Gln Pro Leu Asn Thr Thr Arg Ile Asn Ala Ala
210 215 220
Glu Ile Glu Ser Arg Val Arg Glu Leu Ser Lys Leu Ala Glu Thr Thr
225 230 235 240
Asp Lys Val Lys Gln Gly Phe Trp Glu Glu Phe Glu Thr Leu Gln Gln
245 250 255
Gln Glu Cys Lys Leu Leu Tyr Ser Arg Lys Glu Gly Gln Arg Gln Glu
260 265 270
Asn Lys Asn Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Thr
275 280 285
Arg Val Val Leu His Asp Gly Asp Pro Asn Glu Pro Val Ser Asp Tyr
290 295 300
Ile Asn Ala Asn Ile Ile Met Pro Glu Phe Glu Thr Lys Cys Asn Asn

305 310 315 320
Ser Lys Pro Lys Lys Ser Tyr Ile Ala Thr Gln Gly Cys Leu Gln Asn
325 330 335
Thr Val Asn Asp Phe Trp Arg Met Val Phe Gln Glu Asn Ser Arg Val
340 345 350
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355 360 365
Lys Tyr Trp Pro Asp Glu Tyr Ala Leu Lys Glu Tyr Gly Val Met Arg
370 375 380
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385 390 395 400
Leu Lys Leu Ser Lys Val Gly Gln Gly Asn Thr Glu Arg Thr Val Trp
405 410 415
Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val Pro Ser Asp Pro
420 425 430
Gly Gly Val Leu Asp Phe Leu Glu Glu Val His His Lys Gln Glu Ser
435 440 445
Ile Met Asp Ala Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly
450 455 460
Arg Thr Gly Thr Phe Ile Val Ile Asp Ile Leu Ile Asp Ile Ile Arg
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Glu Lys Gly Val Asp Cys Asp Ile Asp Val Pro Lys Thr Ile Gln Met
485 490 495
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Phe Ile Tyr Met Ala Val Gln His Tyr Ile Glu Thr Leu Gln Arg Arg
515 520 525
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<210> 50
<211> 2338
<212> DNA
<213> Homo sapiens

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tacaatgtag acaacattat attttataga atttgtttga aattgaggaa gcagttaaat 2280
tgtgcgctgt attttgcaga ggattatggg gattcaaatt ctagtaatag gccttttt 2338

<210> 51
<211> 274
<212> DNA
<213> Homo sapiens

<400> 51
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gggaatacgg agagaacggt ctggcaatac cactttcgga cctggccgga ccacggcgtg 180
cccagcgacc ctgggggcgt gctggacttc ctggaggagg tgcaccataa gcaggagagc 240
atcatggatg cagggccggt cgtggtgcac tgca 274

<210> 52
<211> 91
<212> PRT
<213> Homo sapiens

<400> 52
Gln Tyr Trp Pro Asp Glu Tyr Ala Leu Lys Glu Tyr Gly Val Met Arg
1 5 10 15
Val Arg Asn Val Lys Glu Ser Ala Ala His Asp Tyr Thr Leu Arg Glu
20 25 30
Leu Lys Leu Ser Lys Val Gly Gln Gly Asn Thr Glu Arg Thr Val Trp
35 40 45
Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val Pro Ser Asp Pro
50 55 60
Gly Gly Val Leu Asp Phe Leu Glu Glu Val His His Lys Gln Glu Ser
65 70 75 80
Ile Met Asp Ala Gly Pro Val Val Val His Cys
85 90

<210> 53

<211> 90
<212> DNA
<213> Homo sapiens

<400> 53
acggagagaa cggtctggca ataccacttt cggacctggc cggaccacgg cgtgcccagc 60
gaccctgggg gcgtgctgga cttcctggag 90

<210> 54
<211> 2229
<212> DNA
<213> Mus musculus

<400> 54
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gaccagagga gtcgatggca gtttttttagc aaggcccagt aagagtaacc ctggagactt 180
cactctgtct gttagaagaa atggagctgt tacccacatc aagattcaga acactgggga 240
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catggaacac catgggcagc tgaaagagaa gaatggagat gttatcgagc tcaagtaccc 360
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gagccacccc ggagacttcg ttctctccgt gcgcactggt gacgacaaag gggagagcaa 540
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cagctaaatt gtgctctgta ttttctacat tatgggactc aaattctagt tatgggcagg 2160
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ggaatcatg 2229

<210> 55
<211> 597
<212> PRT
<213> Mus musculus

<400> 55
Met Thr Ser Arg Arg Trp Phe His Pro Asn Ile Thr Gly Val Glu Ala
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Glu Asn Leu Leu Leu Thr Arg Gly Val Asp Gly Ser Phe Leu Ala Arg
20 25 30
Pro Ser Lys Ser Asn Pro Gly Asp Phe Thr Leu Ser Val Arg Arg Asn
35 40 45
Gly Ala Val Thr His Ile Lys Ile Gln Asn Thr Gly Asp Tyr Tyr Asp
50 55 60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Ala Glu Leu Val Gln Tyr
65 70 75 80
Tyr Met Glu His His Gly Gln Leu Lys Glu Lys Asn Gly Asp Val Ile
85 90 95
Glu Leu Lys Tyr Pro Leu Asn Cys Ala Asp Pro Thr Ser Glu Arg Trp
100 105 110
Phe His Gly His Leu Ser Gly Lys Glu Ala Glu Lys Leu Leu Thr Glu
115 120 125
Lys Gly Lys His Gly Ser Phe Leu Val Arg Glu Ser Gln Ser His Pro
130 135 140
Gly Asp Phe Val Leu Ser Val Arg Thr Gly Asp Asp Lys Gly Glu Ser
145 150 155 160
Asn Asp Gly Lys Ser Lys Val Thr His Val Met Ile Arg Cys Gln Glu
165 170 175
Leu Lys Tyr Asp Val Gly Gly Gly Glu Arg Phe Asp Ser Leu Thr Asp
180 185 190
Leu Val Glu His Tyr Lys Lys Asn Pro Met Val Glu Thr Leu Gly Thr
195 200 205
Val Leu Gln Leu Lys Gln Pro Leu Asn Thr Thr Arg Ile Asn Ala Ala
210 215 220
Glu Ile Glu Ser Arg Val Arg Glu Leu Ser Lys Leu Ala Glu Thr Thr
225 230 235 240
Asp Lys Val Lys Gln Gly Phe Trp Glu Glu Phe Glu Thr Leu Gln Gln
245 250 255
Gln Glu Cys Lys Leu Leu Tyr Ser Arg Lys Glu Gly Gln Arg Gln Glu
260 265 270
Asn Lys Asn Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Thr
275 280 285
Arg Val Val Leu His Asp Gly Asp Pro Asn Glu Pro Val Ser Asp Tyr
290 295 300
Ile Asn Ala Asn Ile Ile Met Pro Glu Phe Glu Thr Lys Cys Asn Asn
305 310 315 320
Ser Lys Pro Lys Lys Ser Tyr Ile Ala Thr Gln Gly Cys Leu Gln Asn
325 330 335
Thr Val Asn Asp Phe Trp Arg Met Val Phe Gln Glu Asn Ser Arg Val
340 345 350
Ile Val Met Thr Thr Lys Glu Val Glu Arg Gly Lys Ser Lys Cys Val
355 360 365
Lys Tyr Trp Pro Asp Glu Tyr Ala Leu Lys Glu Tyr Gly Val Met Arg
370 375 380
Val Arg Asn Val Lys Glu Ser Ala Ala His Asp Tyr Thr Leu Arg Glu
385 390 395 400
Leu Lys Leu Ser Lys Val Gly Gln Ala Leu Leu Gln Gly Asn Thr Glu
405 410 415
Arg Thr Val Trp Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val
420 425 430
Pro Ser Asp Pro Gly Gly Val Leu Asp Phe Leu Glu Glu Val His His
435 440 445
Lys Gln Glu Ser Ile Val Asp Ala Gly Pro Val Val Val His Cys Ser

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    450                 455                 460
Ala Gly Ile Gly Arg Thr Gly Thr Phe Ile Val Ile Asp Ile Leu Ile
465                 470                 475                 480
Asp Ile Ile Arg Glu Lys Gly Val Asp Cys Asp Ile Asp Val Pro Lys
                485                 490                 495
Thr Ile Gln Met Val Arg Ser Gln Arg Ser Gly Met Val Gln Thr Glu
            500                 505                 510
Ala Gln Tyr Arg Phe Ile Tyr Met Ala Val Gln His Tyr Ile Glu Thr
        515                 520                 525
Leu Gln Arg Arg Ile Glu Glu Glu Gln Lys Ser Lys Arg Lys Gly His
    530                 535                 540
Glu Tyr Thr Asn Ile Lys Tyr Ser Leu Val Asp Gln Thr Ser Gly Asp
545                 550                 555                 560
Gln Ser Pro Leu Pro Pro Cys Thr Pro Thr Pro Pro Cys Ala Glu Met
                565                 570                 575
Arg Glu Asp Ser Ala Arg Val Tyr Glu Asn Val Gly Leu Met Gln Gln
            580                 585                 590
Gln Arg Ser Phe Arg
        595
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<210> 56
<211> 2236
<212> DNA
<213> Rattus norvegicus

<400> 56

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gcacagtcct gcagctcaaa cagcccctca acacaactcg tattaatgcc gctgaaatcg 780
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caccctgtgc ggaaatgcgg gaggacagcg ctcgagtcta tgagaacgtg ggcctcatgc 1860
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agacctgtta agaccg 2236

<210> 57
<211> 583
<212> PRT
<213> Rattus norvegicus

<400> 57
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Glu Asn Leu Leu Leu Thr Arg Gly Val Asp Gly Ser Phe Leu Ala Arg
20 25 30
Pro Ser Lys Ser Asn Pro Gly Asp Phe Thr Leu Ser Val Arg Arg Asn
35 40 45
Gly Ala Val Thr His Ile Lys Ile Gln Asn Thr Gly Asp Tyr Tyr Asp
50 55 60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Pro Glu Leu Val Gln Tyr
65 70 75 80
Tyr Met Glu His His Gly Gln Leu Lys Glu Lys Asn Gly Asp Val Ile
85 90 95
Glu Leu Lys Tyr Pro Leu Asn Cys Ala Asp Pro Thr Ser Glu Arg Trp
100 105 110
Phe His Gly His Leu Ser Gly Lys Glu Ala Glu Lys Leu Leu Thr Glu
115 120 125
Lys Gly Lys His Gly Ser Phe Leu Val Arg Glu Ser Gln Ser His Pro
130 135 140
Gly Asp Phe Val Leu Ser Val Arg Thr Gly Asp Asp Lys Gly Glu Ser
145 150 155 160
Asn Asp Ser Lys Ser Lys Val Thr His Val Met Ile Arg Cys Gln Glu
165 170 175
Leu Lys Tyr Asp Val Gly Gly Gly Glu Arg Phe Asp Ser Leu Thr Asp
180 185 190
Leu Val Glu His Tyr Lys Lys Asn Pro Met Val Glu Thr Leu Gly Thr
195 200 205
Val Leu Gln Leu Lys Gln Pro Leu Asn Thr Thr Arg Ile Asn Ala Ala
210 215 220
Glu Ile Glu Ser Arg Val Arg Glu Leu Ser Lys Leu Ala Glu Thr Thr
225 230 235 240
Asp Lys Val Lys Gln Gly Phe Trp Glu Glu Phe Glu Thr Leu Gln Gln
245 250 255
Gln Glu Cys Lys Leu Leu Tyr Ser Arg Lys Glu Gly Gln Arg Gln Glu
260 265 270
Asn Lys Asn Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Thr
275 280 285
Arg Val Val Leu His Asp Gly Asp Pro Asn Glu Pro Val Ser Asp Tyr
290 295 300
Ile Asn Ala Asn Ile Ile Met Pro Glu Phe Glu Thr Lys Cys Asn Asn
305 310 315 320
Ser Lys Pro Lys Lys Ser Tyr Ile Ala Thr Gln Gly Cys Leu Gln Asn
325 330 335
Thr Val Asn Asp Phe Trp Arg Met Val Phe Gln Glu Asn Ser Arg Val
340 345 350

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Ile Val Met Thr Thr Lys Glu Val Glu Arg Gly Lys Ser Lys Cys Val
        355                 360                 365
Lys Tyr Trp Pro Asp Glu Cys Ala Leu Lys Glu Tyr Gly Val Met Arg
    370                 375                 380
Val Arg Asn Val Arg Glu Ser Ala Ala His Asp Tyr Thr Leu Arg Glu
385                 390                 395                 400
Leu Lys Leu Ser Lys Val Gly Gln Gly Asn Thr Glu Arg Thr Val Trp
                405                 410                 415
Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val Pro Ser Asp Pro
            420                 425                 430
Gly Gly Val Leu Asp Phe Leu Glu Glu Val His His Lys Gln Glu Ser
        435                 440                 445
Ile Val Asp Ala Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly
    450                 455                 460
Arg Thr Gly Thr Phe Ile Val Ile Asp Ile Leu Ile Asp Ile Ile Arg
465                 470                 475                 480
Glu Lys Gly Val Asp Cys Asp Ile Asp Val Pro Lys Thr Ile Gln Met
                485                 490                 495
Val Arg Ser Gln Arg Ser Gly Met Val Gln Thr Glu Ala Gln Tyr Arg
            500                 505                 510
Phe Ile Tyr Met Ala Val Gln His Tyr Ile Glu Thr Leu Gln Arg Arg
        515                 520                 525
Ile Glu Glu Glu Gln Lys Ser Lys Arg Lys Gly His Glu Tyr Thr Asn
    530                 535                 540
Ile Lys Tyr Ser Leu Val Asp Gln Thr Ser Gly Asp Gln Ser Pro Leu
545                 550                 555                 560
Pro Pro Cys Thr Pro Thr Pro Pro Cys Ala Glu Met Arg Glu Asp Ser
                565                 570                 575
Ala Arg Val Tyr Glu Asn Val
            580
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<210> 58
<211> 2090
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 2090
<223> n = A,T,C or G

<400> 58

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<210> 59
<211> 595
<212> PRT
<213> Homo sapiens

<400> 59
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Leu Leu Lys Gly Arg Gly Val His Gly Ser Phe Leu Ala Arg Pro Ser
20 25 30
Arg Lys Asn Gln Gly Asp Phe Ser Leu Ser Val Arg Val Gly Asp Gln
35 40 45
Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp Leu Tyr
50 55 60
Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr Tyr Thr
65 70 75 80
Gln Gln Gln Gly Val Leu Gln Asp Arg Asp Gly Thr Ile Ile His Leu
85 90 95
Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp Tyr His
100 105 110
Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala Lys Gly
115 120 125
Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro Gly Asp
130 135 140
Phe Val Leu Ser Val Leu Ser Asp Gln Pro Lys Ala Gly Pro Gly Ser
145 150 155 160
Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly Arg Tyr
165 170 175
Thr Val Gly Gly Leu Glu Thr Phe Asp Ser Leu Thr Asp Leu Val Glu
180 185 190
His Phe Lys Lys Thr Gly Ile Glu Glu Ala Ser Gly Ala Phe Val Tyr
195 200 205
Leu Arg Gln Pro Tyr Tyr Ala Thr Arg Val Asn Ala Ala Asp Ile Glu
210 215 220
Asn Arg Val Leu Glu Leu Asn Lys Lys Gln Glu Ser Glu Asp Thr Ala
225 230 235 240
Lys Ala Gly Phe Trp Glu Glu Phe Glu Ser Leu Gln Lys Gln Glu Val

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                245                 250                 255
Lys Asn Leu His Gln Arg Leu Glu Gly Gln Arg Pro Glu Asn Lys Gly
            260                 265                 270
Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Ser Arg Val Ile
        275                 280                 285
Leu Gln Gly Arg Asp Ser Asn Ile Pro Gly Ser Asp Tyr Ile Asn Ala
    290                 295                 300
Asn Tyr Ile Lys Asn Gln Leu Leu Gly Pro Asp Glu Asn Ala Lys Thr
305                 310                 315                 320
Tyr Ile Ala Ser Gln Gly Cys Leu Glu Ala Thr Val Asn Asp Phe Trp
                325                 330                 335
Gln Met Ala Trp Gln Glu Asn Ser Arg Val Ile Val Met Thr Thr Arg
            340                 345                 350
Glu Val Glu Lys Gly Arg Asn Lys Cys Val Pro Tyr Trp Pro Glu Val
        355                 360                 365
Gly Met Gln Arg Ala Tyr Gly Pro Tyr Ser Val Thr Asn Cys Gly Glu
    370                 375                 380
His Asp Thr Thr Glu Tyr Lys Leu Arg Thr Leu Gln Val Ser Pro Leu
385                 390                 395                 400
Asp Asn Gly Asp Leu Ile Arg Glu Ile Trp His Tyr Gln Tyr Leu Ser
                405                 410                 415
Trp Pro Asp His Gly Val Pro Ser Glu Pro Gly Gly Val Leu Ser Phe
            420                 425                 430
Leu Asp Gln Ile Asn Gln Arg Gln Glu Ser Leu Pro His Ala Gly Pro
        435                 440                 445
Ile Ile Val His Cys Ser Ala Gly Ile Gly Arg Thr Gly Thr Ile Ile
    450                 455                 460
Val Ile Asp Met Leu Met Glu Asn Ile Ser Thr Lys Gly Leu Asp Cys
465                 470                 475                 480
Asp Ile Asp Ile Gln Lys Thr Ile Gln Met Val Arg Ala Gln Arg Ser
                485                 490                 495
Gly Met Val Gln Thr Glu Ala Gln Tyr Lys Phe Ile Tyr Val Ala Ile
            500                 505                 510
Ala Gln Phe Ile Glu Thr Thr Lys Lys Lys Leu Glu Val Leu Gln Ser
        515                 520                 525
Gln Lys Gly Gln Glu Ser Glu Tyr Gly Asn Ile Thr Tyr Pro Pro Ala
    530                 535                 540
Met Lys Asn Ala His Ala Lys Ala Ser Arg Thr Ser Ser Lys His Lys
545                 550                 555                 560
Glu Asp Val Tyr Glu Asn Leu His Thr Lys Asn Lys Arg Glu Glu Lys
                565                 570                 575
Val Lys Lys Gln Arg Ser Ala Asp Lys Glu Lys Ser Lys Gly Ser Leu
            580                 585                 590
Lys Arg Lys
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<210> 60
<211> 2277
<212> DNA
<213> Homo sapiens

<400> 60
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ggagtccgag gaggaagtgg ctgattactg agcggttctt cctcacctgg cttgggccac 180
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gaggagaaag tgaagaagca gcggtcagca gacaaggaga agagcaaggg ttccctcaag 2040
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tggctgcatc ccccccacct ctccctgacc ctgtatatag cccagccagg ccccaggcag 2220
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<210> 61
<211> 597
<212> PRT
<213> Homo sapiens

<400> 61
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Glu Thr Leu Leu Lys Gly Arg Gly Val His Gly Ser Phe Leu Ala Arg
20 25 30
Pro Ser Arg Lys Asn Gln Gly Asp Phe Ser Leu Ser Val Arg Val Gly
35 40 45
Asp Gln Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp
50 55 60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr
65 70 75 80
Tyr Thr Gln Gln Gln Gly Val Leu Gln Asp Arg Asp Gly Thr Ile Ile
85 90 95
His Leu Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp
100 105 110
Tyr His Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala
115 120 125
Lys Gly Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro
130 135 140

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Gly Asp Phe Val Leu Ser Val Leu Ser Asp Gln Pro Lys Ala Gly Pro
145                 150                 155                 160
Gly Ser Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly
                165                 170                 175
Arg Tyr Thr Val Gly Gly Leu Glu Thr Phe Asp Ser Leu Thr Asp Leu
            180                 185                 190
Val Glu His Phe Lys Lys Thr Gly Ile Glu Glu Ala Ser Gly Ala Phe
        195                 200                 205
Val Tyr Leu Arg Gln Pro Tyr Tyr Ala Thr Arg Val Asn Ala Ala Asp
    210                 215                 220
Ile Glu Asn Arg Val Leu Glu Leu Asn Lys Lys Gln Glu Ser Glu Asp
225                 230                 235                 240
Thr Ala Lys Ala Gly Phe Trp Glu Glu Phe Glu Ser Leu Gln Lys Gln
                245                 250                 255
Glu Val Lys Asn Leu His Gln Arg Leu Glu Gly Gln Arg Pro Glu Asn
            260                 265                 270
Lys Gly Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Ser Arg
        275                 280                 285
Val Ile Leu Gln Gly Arg Asp Ser Asn Ile Pro Gly Ser Asp Tyr Ile
    290                 295                 300
Asn Ala Asn Tyr Ile Lys Asn Gln Leu Leu Gly Pro Asp Glu Asn Ala
305                 310                 315                 320
Lys Thr Tyr Ile Ala Ser Gln Gly Cys Leu Glu Ala Thr Val Asn Asp
                325                 330                 335
Phe Trp Gln Met Ala Trp Gln Glu Asn Ser Arg Val Ile Val Met Thr
            340                 345                 350
Thr Arg Glu Val Glu Lys Gly Arg Asn Lys Cys Val Pro Tyr Trp Pro
        355                 360                 365
Glu Val Gly Met Gln Arg Ala Tyr Gly Pro Tyr Ser Val Thr Asn Cys
    370                 375                 380
Gly Glu His Asp Thr Thr Glu Tyr Lys Leu Arg Thr Leu Gln Val Ser
385                 390                 395                 400
Pro Leu Asp Asn Gly Asp Leu Ile Arg Glu Ile Trp His Tyr Gln Tyr
                405                 410                 415
Leu Ser Trp Pro Asp His Gly Val Pro Ser Glu Pro Gly Gly Val Leu
            420                 425                 430
Ser Phe Leu Asp Gln Ile Asn Gln Arg Gln Glu Ser Leu Pro His Ala
        435                 440                 445
Gly Pro Ile Ile Val His Cys Ser Ala Gly Ile Gly Arg Thr Gly Thr
    450                 455                 460
Ile Ile Val Ile Asp Met Leu Met Glu Asn Ile Ser Thr Lys Gly Leu
465                 470                 475                 480
Asp Cys Asp Ile Asp Ile Gln Lys Thr Ile Gln Met Val Arg Ala Gln
                485                 490                 495
Arg Ser Gly Met Val Gln Thr Glu Ala Gln Tyr Lys Phe Ile Tyr Val
            500                 505                 510
Ala Ile Ala Gln Phe Ile Glu Thr Thr Lys Lys Lys Leu Glu Val Leu
        515                 520                 525
Gln Ser Gln Lys Gly Gln Glu Ser Glu Tyr Gly Asn Ile Thr Tyr Pro
    530                 535                 540
Pro Ala Met Lys Asn Ala His Ala Lys Ala Ser Arg Thr Ser Ser Lys
545                 550                 555                 560
His Lys Glu Asp Val Tyr Glu Asn Leu His Thr Lys Asn Lys Arg Glu
                565                 570                 575
Glu Lys Val Lys Lys Gln Arg Ser Ala Asp Lys Glu Lys Ser Lys Gly
            580                 585                 590
Ser Leu Lys Arg Lys
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<210> 62
<211> 2145
<212> DNA
<213> Homo sapiens

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ccttcctctc cggaagcccc caggatggtg aggtggtttc accgagacct cagtgggctg 180
gatgcagaga ccctgctcaa gggccgaggt gtccacggta gcttcctggc tcggcccagt 240
cgcaagaacc agggtgactt ctcgctctcc gtcagggtgg gggatcaggt gacccatatt 300
cggatccaga actcagggga tttctatgac ctgtatggag gggagaagtt tgcgactctg 360
acagagctgg tggagtacta cactcagcag cagggtgtgg tgcaggaccg cgacggcacc 420
atcatccacc tcaagtaccc gctgaactgc tccgatccca ctagtgagag gtggtaccat 480
ggccacatgt ctggcgggca ggcagagacg ctgctgcagg ccaagggcga gccctggacg 540
tttcttgtgc gtgagagcct cagccagcct ggagacttcg tgctttctgt gctcagtgac 600
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ggtggacgct acacagtggg tggtttggag accttcgaca gcctcacgga cctggtggag 720
catttcaaga agacggggat tgaggaggcc tcaggcgcct ttgtctacct gcggcagccg 780
tactatgcca cgagggtgaa tgcggctgac attgagaacc gagtgttgga actgaacaag 840
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ggccctgatg agaacgctaa gacctacatc gccagccagg gctgtctgga ggccacggtc 1140
aatgacttct ggcagatggc gtggcaggag aacagccgtg tcatcgtcat gaccacccga 1200
gaggtggaga aaggccggaa caaatgcgtc ccatactggc ccgaggtggg catgcagcgt 1260
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tcccgcacct cgtccaaaca caaggaggat gtgtatgaga acctgcacac taagaacaag 1860
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catttcgcga tggacagact cacaacctga acctaggagt gccccattct tttgtaattt 2040
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<210> 63
<211> 595
<212> PRT
<213> Homo sapiens

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Leu Leu Lys Gly Arg Gly Val His Gly Ser Phe Leu Ala Arg Pro Ser
            20   25   30
Arg Lys Asn Gln Gly Asp Phe Ser Leu Ser Val Arg Val Gly Asp Gln
        35   40   45
Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp Leu Tyr

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     50                  55                  60
Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr Tyr Thr
65                  70                  75                  80
Gln Gln Gln Gly Val Val Gln Asp Arg Asp Gly Thr Ile Ile His Leu
                85                  90                  95
Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp Tyr His
            100                 105                 110
Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala Lys Gly
        115                 120                 125
Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro Gly Asp
    130                 135                 140
Phe Val Leu Ser Val Leu Ser Asp Gln Pro Lys Ala Gly Pro Gly Ser
145                 150                 155                 160
Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly Arg Tyr
                165                 170                 175
Thr Val Gly Gly Leu Glu Thr Phe Asp Ser Leu Thr Asp Leu Val Glu
            180                 185                 190
His Phe Lys Lys Thr Gly Ile Glu Glu Ala Ser Gly Ala Phe Val Tyr
        195                 200                 205
Leu Arg Gln Pro Tyr Tyr Ala Thr Arg Val Asn Ala Ala Asp Ile Glu
    210                 215                 220
Asn Arg Val Leu Glu Leu Asn Lys Lys Gln Glu Ser Glu Asp Thr Ala
225                 230                 235                 240
Lys Ala Gly Phe Trp Glu Glu Phe Glu Ser Leu Gln Lys Gln Glu Val
                245                 250                 255
Lys Asn Leu His Gln Arg Leu Glu Gly Gln Arg Pro Glu Asn Lys Gly
            260                 265                 270
Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Ser Arg Val Ile
        275                 280                 285
Leu Gln Gly Arg Asp Ser Asn Ile Pro Gly Ser Asp Tyr Ile Asn Ala
    290                 295                 300
Asn Tyr Ile Lys Asn Gln Leu Leu Gly Pro Asp Glu Asn Ala Lys Thr
305                 310                 315                 320
Tyr Ile Ala Ser Gln Gly Cys Leu Glu Ala Thr Val Asn Asp Phe Trp
                325                 330                 335
Gln Met Ala Trp Gln Glu Asn Ser Arg Val Ile Val Met Thr Thr Arg
            340                 345                 350
Glu Val Glu Lys Gly Arg Asn Lys Cys Val Pro Tyr Trp Pro Glu Val
        355                 360                 365
Gly Met Gln Arg Ala Tyr Gly Pro Tyr Ser Val Thr Asn Cys Gly Glu
    370                 375                 380
His Asp Thr Thr Glu Tyr Lys Leu Arg Thr Leu Gln Val Ser Pro Leu
385                 390                 395                 400
Asp Asn Gly Asp Leu Ile Arg Glu Ile Trp His Tyr Gln Tyr Leu Ser
                405                 410                 415
Trp Pro Asp His Gly Val Pro Ser Glu Pro Gly Gly Val Leu Ser Phe
            420                 425                 430
Leu Asp Gln Ile Asn Gln Arg Gln Glu Ser Leu Pro His Ala Gly Pro
        435                 440                 445
Ile Ile Val His Cys Ser Ala Gly Ile Gly Arg Thr Gly Thr Ile Ile
    450                 455                 460
Val Ile Asp Met Leu Met Glu Asn Ile Ser Thr Lys Gly Leu Asp Cys
465                 470                 475                 480
Asp Ile Asp Ile Gln Lys Thr Ile Gln Met Val Arg Ala Gln Arg Ser
                485                 490                 495
Gly Met Val Gln Thr Glu Ala Gln Tyr Lys Phe Ile Tyr Val Ala Ile
            500                 505                 510
Ala Gln Phe Ile Glu Thr Thr Lys Lys Lys Leu Glu Val Leu Gln Ser
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515 520 525
Gln Lys Gly Gln Glu Ser Glu Tyr Gly Asn Ile Thr Tyr Pro Pro Ala
530 535 540
Met Lys Asn Ala His Ala Lys Ala Ser Arg Thr Ser Ser Lys His Lys
545 550 555 560
Glu Asp Val Tyr Glu Asn Leu His Thr Lys Asn Lys Arg Glu Glu Lys
565 570 575
Val Lys Lys Gln Arg Ser Ala Asp Lys Glu Lys Ser Lys Gly Ser Leu
580 585 590
Lys Arg Lys
595

<210> 64
<211> 2734
<212> DNA
<213> Mus musclus

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aagagaaatt ctgcagcaac tactgaaaga agcccagaaa aagaaactca acagtgagga 180
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ctatcctaca actgtggctc agaggcccaa gaatatcaag aaaaacagat acaaggatat 300
tttgccctat gatcacagcc tggtagagct gtctctgtta acttccgatg aggattccag 360
ttatatcaat gccagcttta ttaagggtgt ctatggaccc aaggcttata ttgctaccca 420
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gaaaaagaaa tctgattata aaatcaggac tctgaaggcc aagttcaata atgaaactcg 660
aattatttac cagtttcatt ataagaattg gccagaccat gatgtgcctt catctataga 720
ccctattctt cagctcatct gggatatgcg ttgttaccaa gaagatgact gtgttcctat 780
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aatactgcta taataataat atcagtaatg aggatatatt ttgtcaatag tcttgaaaag 2640
gaaagcaata tgtgacaaac ttccagcaaa cttgtatttt catattcctt atatttcact 2700
gggaactgcc aataaagttt gtacttcaaa aaaa 2734

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<211> 802
<212> PRT
<213> Mus musculus

<400> 65
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Lys Lys Leu Asn Ser Glu Glu Phe Ala Ser Glu Phe Leu Lys Leu Lys
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Arg Gln Ser Thr Lys Tyr Lys Ala Asp Lys Ile Tyr Pro Thr Thr Val
35 40 45
Ala Gln Arg Pro Lys Asn Ile Lys Lys Asn Arg Tyr Lys Asp Ile Leu
50 55 60
Pro Tyr Asp His Ser Leu Val Glu Leu Ser Leu Leu Thr Ser Asp Glu
65 70 75 80
Asp Ser Ser Tyr Ile Asn Ala Ser Phe Ile Lys Gly Val Tyr Gly Pro
85 90 95
Lys Ala Tyr Ile Ala Thr Gln Gly Pro Leu Ser Thr Thr Leu Leu Asp
100 105 110
Phe Trp Arg Met Ile Trp Glu Tyr Arg Ile Leu Val Ile Val Met Ala
115 120 125
Cys Met Glu Phe Glu Met Gly Lys Lys Lys Cys Glu Arg Tyr Trp Ala
130 135 140
Glu Pro Gly Glu Thr Gln Leu Gln Phe Gly Pro Phe Ser Ile Ser Cys
145 150 155 160
Glu Ala Glu Lys Lys Lys Ser Asp Tyr Lys Ile Arg Thr Leu Lys Ala
165 170 175
Lys Phe Asn Asn Glu Thr Arg Ile Ile Tyr Gln Phe His Tyr Lys Asn
180 185 190
Trp Pro Asp His Asp Val Pro Ser Ser Ile Asp Pro Ile Leu Gln Leu
195 200 205
Ile Trp Asp Met Arg Cys Tyr Gln Glu Asp Asp Cys Val Pro Ile Cys
210 215 220
Ile His Cys Ser Ala Gly Cys Gly Arg Thr Gly Val Ile Cys Ala Val
225 230 235 240
Asp Tyr Thr Trp Met Leu Leu Lys Asp Gly Ile Ile Pro Lys Asn Phe
245 250 255
Ser Val Phe Asn Leu Ile Gln Glu Met Arg Thr Gln Arg Pro Ser Leu
260 265 270
Val Gln Thr Gln Glu Gln Tyr Glu Leu Val Tyr Ser Ala Val Leu Glu
275 280 285
Leu Phe Lys Arg His Met Asp Val Ile Ser Asp Asn His Leu Gly Arg
290 295 300
Glu Ile Gln Ala Gln Cys Ser Ile Pro Glu Gln Ser Leu Thr Val Glu
305 310 315 320
Ala Asp Ser Cys Pro Leu Asp Leu Pro Lys Asn Ala Met Arg Asp Val
325 330 335
Lys Thr Thr Asn Gln His Ser Lys Gln Gly Ala Glu Ala Glu Ser Thr
340 345 350

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Gly Gly Ser Ser Leu Gly Leu Arg Thr Ser Thr Met Asn Ala Glu Glu
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Glu Leu Val Leu His Ser Ala Lys Ser Ser Pro Ser Phe Asn Cys Leu
    370                 375                 380
Glu Leu Asn Cys Gly Cys Asn Asn Lys Ala Val Ile Thr Arg Asn Gly
385                 390                 395                 400
Gln Ala Arg Ala Ser Pro Val Val Gly Glu Pro Leu Gln Lys Tyr Gln
                405                 410                 415
Ser Leu Asp Phe Gly Ser Met Leu Phe Gly Ser Cys Pro Ser Ala Leu
            420                 425                 430
Pro Ile Asn Thr Ala Asp Arg Tyr His Asn Ser Lys Gly Pro Val Lys
        435                 440                 445
Arg Thr Lys Ser Thr Pro Phe Glu Leu Ile Gln Gln Arg Lys Thr Asn
    450                 455                 460
Asp Leu Ala Val Gly Asp Gly Phe Ser Cys Leu Glu Ser Gln Leu His
465                 470                 475                 480
Glu His Tyr Ser Leu Arg Glu Leu Gln Val Gln Arg Val Ala His Val
                485                 490                 495
Ser Ser Glu Glu Leu Asn Tyr Ser Leu Pro Gly Ala Cys Asp Ala Ser
            500                 505                 510
Cys Val Pro Arg His Ser Pro Gly Ala Leu Arg Val His Leu Tyr Thr
        515                 520                 525
Ser Leu Ala Glu Asp Pro Tyr Phe Ser Ser Ser Pro Pro Asn Ser Ala
    530                 535                 540
Asp Ser Lys Met Ser Phe Asp Leu Pro Glu Lys Gln Asp Gly Ala Thr
545                 550                 555                 560
Ser Pro Gly Ala Leu Leu Pro Ala Ser Ser Thr Thr Ser Phe Phe Tyr
                565                 570                 575
Ser Asn Pro His Asp Ser Leu Val Met Asn Thr Leu Thr Ser Phe Ser
            580                 585                 590
Pro Pro Leu Asn Gln Glu Thr Ala Val Glu Ala Pro Ser Arg Arg Thr
        595                 600                 605
Asp Asp Glu Ile Pro Pro Pro Leu Pro Glu Arg Thr Pro Glu Ser Phe
    610                 615                 620
Ile Val Val Glu Glu Ala Gly Glu Pro Ser Pro Arg Val Thr Glu Ser
625                 630                 635                 640
Leu Pro Leu Val Val Thr Phe Gly Ala Ser Pro Glu Cys Ser Gly Thr
                645                 650                 655
Ser Glu Met Lys Ser His Asp Ser Val Gly Phe Thr Pro Ser Lys Asn
            660                 665                 670
Val Lys Leu Arg Ser Pro Lys Ser Asp Arg His Gln Asp Gly Ser Pro
        675                 680                 685
Pro Pro Pro Leu Pro Glu Arg Thr Leu Glu Ser Phe Phe Leu Ala Asp
    690                 695                 700
Glu Asp Cys Ile Gln Ala Gln Ala Val Gln Thr Ser Ser Thr Ser Tyr
705                 710                 715                 720
Pro Glu Thr Thr Glu Asn Ser Thr Ser Ser Lys Gln Thr Leu Arg Thr
                725                 730                 735
Pro Gly Lys Ser Phe Thr Arg Ser Lys Ser Leu Lys Ile Phe Arg Asn
            740                 745                 750
Met Lys Lys Ser Val Cys Asn Ser Ser Ser Pro Ser Lys Pro Thr Glu
        755                 760                 765
Arg Val Gln Pro Lys Asn Ser Ser Ser Phe Leu Asn Phe Gly Phe Gly
    770                 775                 780
Asn Arg Phe Ser Lys Pro Lys Gly Pro Arg Asn Pro Pro Ser Ala Trp
785                 790                 795                 800
Asn Met
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<210> 66
<211> 3717
<212> DNA
<213> Homo sapiens

<400> 66
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<210> 71
<211> 525
<212> PRT
<213> Rattus norvegicus

<400> 71

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			20					25					30		
Ala	Ser	Arg	Ala	Gly	Gly	Leu	Ser	Pro	Val	Thr	Asn	Leu	Thr	Val	Thr
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Val	Arg	Asn	Ser	Ser	Ser	Leu	Gln	Arg	Met	Gly	Ser	Ser	Glu	Ser	Thr
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Asp	Ser	Gly	Phe	Cys	Leu	Asp	Ser	Pro	Gly	Pro	Leu	Asp	Ser	Lys	Glu
				85					90					95	
Asn	Leu	Glu	Ile	Ser	Leu	Arg	Arg	Ile	Asn	Cys	Leu	Pro	Gln	Lys	Leu
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Leu	Gly	Cys	Ser	Pro	Ala	Leu	Lys	Arg	Ser	His	Ser	Asp	Ser	Leu	Asp
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His	Asp	Ile	Phe	Gln	Leu	Ile	Asp	Gln	Asp	Glu	Asn	Lys	Glu	Asn	Glu
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Trp	Thr	Ala	Pro	Leu	Val	Met	Arg	Arg	Pro	Thr	Asn	Leu	Ala	Asp	Arg
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Cys	Gly	Leu	Phe	Asp	Ser	Pro	Ser	Pro	Cys	Ser	Ser	Thr	Ser	Ser	Cys
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Ser	Thr	Arg	Ala	Val	Lys	Arg	Ala	Asp	Arg	Ser	His	Glu	Glu	Ser	Pro
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Gly Lys His Gln Asp Leu Lys Tyr Ile Ser Pro Glu Ile Met Ala Ser
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Val Leu Asn Gly Lys Phe Ala Asn Leu Ile Lys Glu Phe Val Ile Ile
    370                 375                 380
Asp Cys Arg Tyr Pro Tyr Glu Tyr Glu Gly Gly His Ile Lys Gly Ala
385                 390                 395                 400
Val Asn Leu His Met Glu Glu Glu Val Glu Glu Phe Leu Leu Lys Lys
                405                 410                 415
Pro Ile Val Pro Ala Asp Gly Lys Arg Val Ile Val Val Phe His Cys
            420                 425                 430
Glu Phe Ser Ser Glu Arg Gly Pro Arg Met Cys Arg Tyr Val Arg Glu
        435                 440                 445
Arg Asp Arg Leu Gly Asn Glu Tyr Pro Lys Leu His Tyr Pro Glu Leu
    450                 455                 460
Tyr Val Leu Lys Gly Gly Tyr Lys Glu Phe Phe Leu Lys Cys Gln Ser
465                 470                 475                 480
His Cys Glu Pro Pro Ser Tyr Arg Pro Met His His Glu Asp Phe Lys
                485                 490                 495
Glu Asp Leu Lys Lys Phe Arg Thr Lys Ser Arg Thr Trp Ala Gly Glu
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<210> 72
<211> 2804
<212> DNA
<213> Rattus norvegicus

<400> 72

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<210> 73
<211> 574
<212> PRT
<213> Rattus norvegicus

<400> 73

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Gly	Phe	Gly	Ser	Asp	Gly	Leu	Leu	Gly	Ser	Pro	Glu	Arg	Ala	Ala	Ser
		35					40					45			
Ser	Ser	Pro	Val	Thr	Thr	Leu	Thr	Gln	Thr	Met	Tyr	Asn	Leu	Ala	Gly
	50					55					60				
Leu	Gly	Ser	Glu	Thr	Pro	Lys	Thr	Gln	Val	Gly	Ser	Leu	Ser	Phe	Gln
65					70					75					80
Asn	Arg	Leu	Thr	Asp	Leu	Ser	Leu	Ser	Arg	Arg	Thr	Ser	Glu	Cys	Ser
				85					90					95	
Leu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Asp	Ala	Gly	Leu	Cys	Met	Asp
			100					105					110		
Ser	Pro	Ser	Pro	Met	Asp	Pro	Gln	Thr	Ala	Glu	Arg	Thr	Phe	Glu	Gln
		115					120					125			
Ala	Ile	Gln	Ala	Ala	Ser	Arg	Val	Ile	Gln	Lys	Met	Gln	Phe	Thr	Ile
	130					135					140				
Lys	Ala	Ser	Val	Phe	Ala	Ser	Glu	Ala	Ala	Gly	His	Ser	Pro	Val	Leu
145					150					155					160
Gln	Asn	Ile	Thr	Asn	Ser	Gln	Ala	Leu	Asp	Ser	Trp	Glu	Lys	Asp	Glu
				165					170					175	
Ala	Gly	Tyr	Arg	Ala	Ala	Ser	Ser	Pro	Gly	Glu	Asp	Lys	Glu	Asn	Asp
			180					185					190		
Gly	Tyr	Ile	Phe	Lys	Met	Pro	Gln	Lys	Leu	Pro	His	Ser	Ser	Ser	Ala
		195					200					205			
Arg	Ala	Leu	Ala	Glu	Trp	Ala	Ser	Arg	Arg	Glu	Ala	Phe	Thr	Gln	Arg
	210					215					220				

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                245                 250                 255
Val Glu Arg Ala Cys Glu Glu Asp Asp Gly Phe Val Asp Ile Leu Glu
            260                 265                 270
Ser Asp Leu Lys Asp Asp Asp Met Val Pro Ala Gly Met Glu Asn Leu
        275                 280                 285
Ile Ser Ala Pro Leu Val Lys Lys Leu Asp Lys Glu Glu Glu Gln Asp
    290                 295                 300
Leu Ile Met Phe Ser Lys Cys Gln Arg Leu Phe Arg Ser Pro Ser Met
305                 310                 315                 320
Pro Cys Ser Val Ile Arg Pro Ile Leu Lys Arg Leu Glu Arg Pro His
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Asp Arg Asp Val Pro Val Leu Ser Lys Arg Arg Lys Ser Gly Thr Pro
            340                 345                 350
Leu Glu Glu Gln Gln Leu Glu Glu Pro Lys Ala Arg Val Phe Arg Ser
        355                 360                 365
Lys Ser Leu Cys His Glu Ile Glu Ser Ile Leu Asp Ser Asp His Arg
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Gly Leu Ile Gly Asp Tyr Ser Lys Ala Phe Leu Leu Gln Thr Val Asp
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Gly Lys His Gln Asp Leu Lys Tyr Ile Ser Pro Glu Thr Met Val Ala
                405                 410                 415
Leu Leu Thr Gly Lys Phe Ser Asn Ile Val Glu Lys Phe Val Ile Val
            420                 425                 430
Asp Cys Arg Tyr Pro Tyr Glu Tyr Glu Gly Gly His Ile Lys Asn Ala
        435                 440                 445
Val Asn Leu Pro Leu Glu Pro Asp Ala Glu Thr Phe Leu Leu Lys His
    450                 455                 460
Pro Ile Thr Pro Cys Asn Leu Asp Lys Arg Ile Ile Leu Ile Phe His
465                 470                 475                 480
Cys Glu Phe Ser Ser Glu Arg Gly Pro Arg Met Cys Arg Phe Ile Arg
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Glu Arg Asp Arg Ala Ala Asn Asp Tyr Pro Ser Leu Tyr Tyr Pro Glu
            500                 505                 510
Met Tyr Ile Leu Lys Gly Gly Tyr Lys Glu Phe Phe Pro Gln His Pro
        515                 520                 525
Asn Phe Cys Glu Pro Gln Asp Tyr Arg Pro Met Asn His Ala Ala Phe
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<210> 74
<211> 2935
<212> DNA
<213> Mus musculus

<400> 74

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<210> 75
<211> 576
<212> PRT
<213> Mus musculus

<400> 75
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35 40 45
Ser Ser Pro Val Thr Thr Leu Thr Gln Thr Met His Asn Leu Ala Gly
50 55 60

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Leu Ser Ser Glu Ser Ser Glu Ser Ser Asp Ala Gly Leu Cys Met Asp
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Ser Pro Ser Pro Val Asp Pro Gln Met Ala Glu Arg Thr Phe Glu Gln
        115                 120                 125
Ala Ile Gln Ala Ala Ser Arg Val Ile Gln Asn Glu Gln Phe Thr Ile
    130                 135                 140
Lys Arg Phe Arg Ser Leu Pro Val Arg Leu Leu Glu His Ser Pro Val
145                 150                 155                 160
Leu Gln Ser Ile Thr Asn Ser Arg Ala Leu Asp Ser Trp Arg Lys Thr
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Lys Met Glu Val Glu Glu Leu Ser Pro Val Ala Gln Ser Ser Ser Leu
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Ser Met Pro Cys Ser Val Ile Arg Pro Ile Leu Lys Arg Leu Glu Arg
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Thr Pro Leu Glu Glu Gln Gln Leu Glu Glu Pro Lys Ala Arg Val Phe
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Arg Ser Lys Ser Leu Cys His Glu Ile Glu Asn Ile Leu Asp Ser Asp
    370                 375                 380
His Arg Gly Leu Ile Gly Asp Tyr Ser Lys Ala Phe Leu Leu Gln Thr
385                 390                 395                 400
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Val Ala Leu Leu Thr Gly Lys Phe Ser Asn Ile Val Glu Lys Phe Val
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Ile Val Asp Cys Arg Tyr Pro Tyr Glu Tyr Glu Gly Gly His Ile Lys
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Asn Ala Val Asn Leu Pro Leu Glu Arg Asp Ala Glu Thr Phe Leu Leu
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Gln Arg Pro Ile Met Pro Cys Ser Leu Asp Lys Arg Ile Ile Leu Ile
465                 470                 475                 480
Phe His Cys Glu Phe Ser Ser Glu Arg Gly Pro Arg Met Cys Arg Phe
                485                 490                 495
Ile Arg Glu Arg Asp Arg Ala Ala Asn Asp Tyr Pro Ser Leu Tyr Tyr
            500                 505                 510
Pro Glu Met Tyr Ile Leu Lys Gly Gly Tyr Lys Glu Phe Phe Pro Gln
        515                 520                 525
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His Pro Asn Phe Cys Glu Pro Gln Asp Tyr Arg Pro Met Asn His Glu
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Ala Phe Arg Asp Glu Leu Arg Asn Phe Arg Leu Lys Thr Arg Ser Trp
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Ala Gly Glu Arg Ser Arg Arg Glu Leu Cys Ser Arg Leu Gln Asp Gln
565 570 575

<210> 76
<211> 3578
<212> DNA
<213> Homo sapiens

<400> 76
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<210> 77
<211> 539
<212> PRT
<213> Homo sapiens

<400> 77
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Leu Leu Gly Ser His Gly Leu Leu Gly Ser Pro Val Arg Ala Ala Ala
35 40 45
Ser Ser Pro Val Thr Thr Leu Thr Gln Thr Met His Asp Leu Ala Gly
50 55 60
Leu Gly Ser Glu Thr Pro Lys Ser Gln Val Gly Thr Leu Leu Phe Arg
65 70 75 80
Ser Arg Ser Arg Leu Thr His Leu Ser Leu Ser Arg Arg Ala Ser Glu
85 90 95
Ser Ser Leu Ser Ser Glu Ser Ser Glu Ser Ser Asp Ala Gly Leu Cys
100 105 110
Met Asp Ser Pro Ser Pro Met Asp Pro His Met Ala Glu Gln Thr Phe
115 120 125
Glu Gln Ala Ile Gln Ala Ala Ser Arg Ile Ile Arg Asn Glu Gln Phe
130 135 140
Ala Ile Arg Arg Phe Gln Ser Met Pro Asp Gly Phe Val Phe Lys Met
145 150 155 160
Pro Trp Lys Pro Thr His Pro Ser Ser Thr His Ala Leu Ala Glu Trp
165 170 175
Ala Ser Arg Arg Glu Ala Phe Ala Gln Arg Pro Ser Ser Ala Pro Asp
180 185 190
Leu Met Cys Leu Ser Pro Asp Arg Lys Met Glu Val Glu Glu Leu Ser
195 200 205
Pro Leu Ala Leu Gly Arg Phe Ser Leu Thr Pro Ala Glu Gly Asp Thr
210 215 220
Glu Glu Asp Asp Gly Phe Val Asp Ile Leu Glu Ser Asp Leu Lys Asp
225 230 235 240
Asp Asp Ala Val Pro Pro Gly Met Glu Ser Leu Ile Ser Ala Pro Leu
245 250 255
Val Lys Thr Leu Glu Lys Glu Glu Glu Lys Asp Leu Val Met Tyr Ser
260 265 270
Lys Cys Gln Arg Leu Phe Arg Ser Pro Ser Met Pro Cys Ser Val Ile

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        275                 280                 285
Arg Pro Ile Leu Lys Arg Leu Glu Arg Pro Gln Asp Arg Asp Thr Pro
    290                 295                 300
Val Gln Asn Lys Arg Arg Arg Ser Val Thr Pro Pro Glu Glu Gln Gln
305                 310                 315                 320
Glu Ala Glu Glu Pro Lys Ala Arg Val Leu Arg Ser Lys Ser Leu Cys
                325                 330                 335
His Asp Glu Ile Glu Asn Leu Leu Asp Ser Asp His Arg Glu Leu Ile
            340                 345                 350
Gly Asp Tyr Ser Lys Ala Phe Leu Leu Gln Thr Val Asp Gly Lys His
        355                 360                 365
Gln Asp Leu Lys Tyr Ile Ser Pro Glu Thr Met Val Ala Leu Leu Thr
    370                 375                 380
Gly Lys Phe Ser Asn Ile Val Asp Lys Phe Val Ile Val Asp Cys Arg
385                 390                 395                 400
Tyr Pro Tyr Glu Tyr Glu Gly Gly His Ile Lys Thr Ala Val Asn Leu
                405                 410                 415
Pro Leu Glu Arg Asp Ala Glu Ser Phe Leu Leu Lys Ser Pro Ile Ala
            420                 425                 430
Pro Cys Ser Leu Asp Lys Arg Val Ile Leu Ile Phe His Cys Glu Phe
        435                 440                 445
Ser Ser Glu Arg Gly Pro Arg Met Cys Arg Phe Ile Arg Glu Arg Asp
    450                 455                 460
Arg Ala Val Asn Asp Tyr Pro Ser Leu Tyr Tyr Pro Glu Met Tyr Ile
465                 470                 475                 480
Leu Lys Gly Gly Tyr Lys Glu Phe Phe Pro Gln His Pro Asn Phe Cys
                485                 490                 495
Glu Pro Gln Asp Tyr Arg Pro Met Asn His Glu Ala Phe Lys Asp Glu
            500                 505                 510
Leu Lys Thr Phe Arg Leu Lys Thr Arg Ser Trp Ala Gly Glu Arg Ser
        515                 520                 525
Arg Arg Glu Leu Cys Ser Arg Leu Gln Asp Gln
    530                 535
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<210> 78
<211> 2940
<212> DNA
<213> Homo sapiens

<400> 78

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<210> 79
<211> 566
<212> PRT
<213> Homo sapiens

<400> 79
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Leu Leu Gly Ser His Gly Leu Leu Gly Ser Pro Val Arg Ala Ala Ala
35 40 45
Ser Ser Pro Val Thr Thr Leu Thr Gln Thr Met His Asp Leu Ala Gly
50 55 60
Leu Gly Ser Arg Ser Arg Leu Thr His Leu Ser Leu Ser Arg Arg Ala
65 70 75 80
Ser Glu Ser Ser Leu Ser Ser Glu Ser Ser Glu Ser Ser Asp Ala Gly
85 90 95
Leu Cys Met Asp Ser Pro Ser Pro Met Asp Pro His Met Ala Glu Gln
100 105 110
Thr Phe Glu Gln Ala Ile Gln Ala Ala Ser Arg Ile Ile Arg Asn Glu
115 120 125
Gln Phe Ala Ile Arg Arg Phe Gln Ser Met Pro Val Arg Leu Leu Gly
130 135 140

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His Ser Pro Val Leu Arg Asn Ile Thr Asn Ser Gln Ala Pro Asp Gly
145                 150                 155                 160
Arg Arg Lys Ser Glu Ala Gly Ser Gly Ala Ala Ser Ser Ser Gly Glu
                165                 170                 175
Asp Lys Glu Asn Asp Gly Phe Val Phe Lys Met Pro Trp Lys Pro Thr
            180                 185                 190
His Pro Ser Ser Thr His Ala Leu Ala Glu Trp Ala Ser Arg Arg Glu
        195                 200                 205
Ala Phe Ala Gln Arg Pro Ser Ser Ala Pro Asp Leu Met Cys Leu Ser
    210                 215                 220
Pro Asp Arg Lys Met Glu Val Glu Glu Leu Ser Pro Leu Ala Leu Gly
225                 230                 235                 240
Arg Phe Ser Leu Thr Pro Ala Glu Gly Asp Thr Glu Glu Asp Asp Gly
                245                 250                 255
Phe Val Asp Ile Leu Glu Ser Asp Leu Lys Asp Asp Asp Ala Val Pro
            260                 265                 270
Pro Gly Met Glu Ser Leu Ile Ser Ala Pro Leu Val Lys Thr Leu Glu
        275                 280                 285
Lys Glu Glu Glu Lys Asp Leu Val Met Tyr Ser Lys Cys Gln Arg Leu
    290                 295                 300
Phe Arg Ser Pro Ser Met Pro Cys Ser Val Ile Arg Pro Ile Leu Lys
305                 310                 315                 320
Arg Leu Glu Arg Pro Gln Asp Arg Asp Thr Pro Val Gln Asn Lys Arg
                325                 330                 335
Arg Arg Ser Val Thr Pro Pro Glu Glu Gln Gln Glu Ala Glu Glu Pro
            340                 345                 350
Lys Ala Arg Val Leu Arg Ser Lys Ser Leu Cys His Asp Glu Ile Glu
        355                 360                 365
Asn Leu Leu Asp Ser Asp His Arg Glu Leu Ile Gly Asp Tyr Ser Lys
    370                 375                 380
Ala Phe Leu Leu Gln Thr Val Asp Gly Lys His Gln Asp Leu Lys Tyr
385                 390                 395                 400
Ile Ser Pro Glu Thr Met Val Ala Leu Leu Thr Gly Lys Phe Ser Asn
                405                 410                 415
Ile Val Asp Lys Phe Val Ile Val Asp Cys Arg Tyr Pro Tyr Glu Tyr
            420                 425                 430
Glu Gly Gly His Ile Lys Thr Ala Val Asn Leu Pro Leu Glu Arg Asp
        435                 440                 445
Ala Glu Ser Phe Leu Leu Lys Ser Pro Ile Ala Pro Cys Ser Leu Asp
    450                 455                 460
Lys Arg Val Ile Leu Ile Phe His Cys Glu Phe Ser Ser Glu Arg Gly
465                 470                 475                 480
Pro Arg Met Cys Arg Phe Ile Arg Glu Arg Asp Arg Ala Val Asn Asp
                485                 490                 495
Tyr Pro Ser Leu Tyr Tyr Pro Glu Met Tyr Ile Leu Lys Gly Gly Tyr
            500                 505                 510
Lys Glu Phe Phe Pro Gln His Pro Asn Phe Cys Glu Pro Gln Asp Tyr
        515                 520                 525
Arg Pro Met Asn His Glu Ala Phe Lys Asp Glu Leu Lys Thr Phe Arg
    530                 535                 540
Leu Lys Thr Arg Ser Trp Ala Gly Glu Arg Ser Arg Arg Glu Leu Cys
545                 550                 555                 560
Ser Arg Leu Gln Asp Gln
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<210> 80
<211> 2115

<212> DNA
<213> Homo sapiens

<400> 80
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<210> 81
<211> 473
<212> PRT
<213> Homo sapiens

<400> 81
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20 25 30
Leu Glu Arg Asp Thr Ser Phe Thr Val Cys Pro Asp Val Pro Arg Thr
35 40 45
Pro Val Gly Lys Phe Leu Gly Asp Ser Ala Asn Leu Ser Ile Leu Ser
50 55 60
Gly Gly Thr Pro Lys Cys Cys Leu Asp Leu Ser Asn Leu Ser Ser Gly
65 70 75 80
Glu Ile Thr Ala Thr Gln Leu Thr Thr Ser Ala Asp Leu Asp Glu Thr

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                85                  90                  95
Gly His Leu Asp Ser Ser Gly Leu Gln Glu Val His Leu Ala Gly Met
            100                 105                 110
Asn His Asp Gln His Leu Met Lys Cys Ser Pro Ala Gln Leu Leu Cys
        115                 120                 125
Ser Thr Pro Asn Gly Leu Asp Arg Gly His Arg Lys Arg Asp Ala Met
    130                 135                 140
Cys Ser Ser Ser Ala Asn Lys Glu Asn Asp Asn Gly Asn Leu Val Asp
145                 150                 155                 160
Ser Glu Met Lys Tyr Leu Gly Ser Pro Ile Thr Thr Val Pro Lys Leu
                165                 170                 175
Asp Lys Asn Pro Asn Leu Gly Glu Asp Gln Ala Glu Glu Ile Ser Asp
            180                 185                 190
Glu Leu Met Glu Phe Ser Leu Lys Asp Gln Glu Ala Lys Val Ser Arg
        195                 200                 205
Ser Gly Leu Tyr Arg Ser Pro Ser Met Pro Glu Asn Leu Asn Arg Pro
    210                 215                 220
Arg Leu Lys Gln Val Glu Lys Phe Lys Asp Asn Thr Ile Pro Asp Lys
225                 230                 235                 240
Val Lys Lys Lys Tyr Phe Ser Gly Gln Gly Lys Leu Arg Lys Gly Leu
                245                 250                 255
Cys Leu Lys Lys Thr Val Ser Leu Cys Asp Ile Thr Ile Thr Gln Met
            260                 265                 270
Leu Glu Glu Asp Ser Asn Gln Gly His Leu Ile Gly Asp Phe Ser Lys
        275                 280                 285
Val Cys Ala Leu Pro Thr Val Ser Gly Lys His Gln Asp Leu Lys Tyr
    290                 295                 300
Val Asn Pro Glu Thr Val Ala Ala Leu Leu Ser Gly Lys Phe Gln Gly
305                 310                 315                 320
Leu Ile Glu Lys Phe Tyr Val Ile Asp Cys Arg Tyr Pro Tyr Glu Tyr
                325                 330                 335
Leu Gly Gly His Ile Gln Gly Ala Leu Asn Leu Tyr Ser Gln Glu Glu
            340                 345                 350
Leu Phe Asn Phe Phe Leu Lys Lys Pro Ile Val Pro Leu Asp Thr Gln
        355                 360                 365
Lys Arg Ile Ile Ile Val Phe His Cys Glu Phe Ser Ser Glu Arg Gly
    370                 375                 380
Pro Arg Met Cys Arg Cys Leu Arg Glu Glu Asp Arg Ser Leu Asn Gln
385                 390                 395                 400
Tyr Pro Ala Leu Tyr Tyr Pro Glu Leu Tyr Ile Leu Lys Gly Gly Tyr
                405                 410                 415
Arg Asp Phe Phe Pro Glu Tyr Met Glu Leu Cys Glu Pro Gln Ser Tyr
            420                 425                 430
Cys Pro Met His His Gln Asp His Lys Thr Glu Leu Leu Arg Cys Arg
        435                 440                 445
Ser Gln Ser Lys Val Gln Glu Gly Glu Arg Gln Leu Arg Glu Gln Ile
    450                 455                 460
Ala Leu Leu Val Lys Asp Met Ser Pro
465                 470
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<210> 82
<211> 1896
<212> DNA
<213> Homo sapiens

<400> 82
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taactacctc ctttccccta gatttccttt cattctgctc aagtcttcgc ctgtgtccga 180
tccctatcta ctttctctcc tcttgtagca agcctcagac tccaggcttg agctaggttt 240
tgtttttctc ctggtgagaa ttcgaagacc atgtctacgg aactcttctc atccacaaga 300
gaggaaggaa gctctggctc aggacccagt tttaggtcta atcaaaggaa aatgttaaac 360
ctgctcctgg agagagacac ttcctttacc gtctgtccag atgtccctag aactccagtg 420
ggcaaatttc ttggtgattc tgcaaaccta agcattttgt ctgggtcacc tggattcttc 480
aggacttcag gaagtgcatt tagctgggat gacaatggaa acttggtgga cagtgaaatg 540
aaatatttgg gcagtcccat tactactgtt ccaaaattgg ataaaaatcc aaacctagga 600
gaagaccagg cagaagagat ttcagatgaa ttaatggagt tttccctgaa agatcaagaa 660
gcaaaggtga gcagaagtgg cctatatcgc tccccgtcga tgccagagaa cttgaacagg 720
ccaagactga agcaggtgga aaaattcaag gacaacacaa taccagataa agttaaaaaa 780
aagtattttt ctggccaagg aaagctcagg aagggcttat gtttaaagaa gacagtctct 840
ctgtgtgaca ttactatcac tcagatgctg gaggaagatt ctaaccaggg gcacctgatt 900
ggtgattttt ccaaggtatg tgcgctgcca accgtgtcag ggaaacacca agatctgaag 960
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aagttttatg tcattgattg tcgctatcca tatgagtatc tgggaggaca catccaggga 1080
gccttaaact tatatagtca ggaagaactg tttaacttct ttctgaagaa gcccatcgtc 1140
cctttggaca cccagaagag aataatcatc gtgttccact gtgaattctc ctcagagagg 1200
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ttgctgaggt gtcgaagcca gagcaaagtg caggaagggg agcggcagct gcgggagcag 1440
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tgcaagagcg ttgtctacct tctttctttg tattttcctt ctttgtttcc ccctctttct 1860
tttttaaaaa tggaaaaata aacactacag aatgag 1896

<210> 83
<211> 400
<212> PRT
<213> Homo sapiens

<400> 83
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Ser Gly Pro Ser Phe Arg Ser Asn Gln Arg Lys Met Leu Asn Leu Leu
20 25 30
Leu Glu Arg Asp Thr Ser Phe Thr Val Cys Pro Asp Val Pro Arg Thr
35 40 45
Pro Val Gly Lys Phe Leu Gly Asp Ser Ala Asn Leu Ser Ile Leu Ser
50 55 60
Gly Ser Pro Gly Phe Phe Arg Thr Ser Gly Ser Ala Phe Ser Trp Asp
65 70 75 80
Asp Asn Gly Asn Leu Val Asp Ser Glu Met Lys Tyr Leu Gly Ser Pro
85 90 95
Ile Thr Thr Val Pro Lys Leu Asp Lys Asn Pro Asn Leu Gly Glu Asp
100 105 110
Gln Ala Glu Glu Ile Ser Asp Glu Leu Met Glu Phe Ser Leu Lys Asp
115 120 125
Gln Glu Ala Lys Val Ser Arg Ser Gly Leu Tyr Arg Ser Pro Ser Met
130 135 140
Pro Glu Asn Leu Asn Arg Pro Arg Leu Lys Gln Val Glu Lys Phe Lys
145 150 155 160

Asp Asn Thr Ile Pro Asp Lys Val Lys Lys Lys Tyr Phe Ser Gly Gln
165 170 175
Gly Lys Leu Arg Lys Gly Leu Cys Leu Lys Lys Thr Val Ser Leu Cys
180 185 190
Asp Ile Thr Ile Thr Gln Met Leu Glu Glu Asp Ser Asn Gln Gly His
195 200 205
Leu Ile Gly Asp Phe Ser Lys Val Cys Ala Leu Pro Thr Val Ser Gly
210 215 220
Lys His Gln Asp Leu Lys Tyr Val Asn Pro Glu Thr Val Ala Ala Leu
225 230 235 240
Leu Ser Gly Lys Phe Gln Gly Leu Ile Glu Lys Phe Tyr Val Ile Asp
245 250 255
Cys Arg Tyr Pro Tyr Glu Tyr Leu Gly Gly His Ile Gln Gly Ala Leu
260 265 270
Asn Leu Tyr Ser Gln Glu Glu Leu Phe Asn Phe Phe Leu Lys Lys Pro
275 280 285
Ile Val Pro Leu Asp Thr Gln Lys Arg Ile Ile Ile Val Phe His Cys
290 295 300
Glu Phe Ser Ser Glu Arg Gly Pro Arg Met Cys Arg Cys Leu Arg Glu
305 310 315 320
Glu Asp Arg Ser Leu Asn Gln Tyr Pro Ala Leu Tyr Tyr Pro Glu Leu
325 330 335
Tyr Ile Leu Lys Gly Gly Tyr Arg Asp Phe Phe Pro Glu Tyr Met Glu
340 345 350
Leu Cys Glu Pro Gln Ser Tyr Cys Pro Met His His Gln Asp His Lys
355 360 365
Thr Glu Leu Leu Arg Cys Arg Ser Gln Ser Lys Val Gln Glu Gly Glu
370 375 380
Arg Gln Leu Arg Glu Gln Ile Ala Leu Leu Val Lys Asp Met Ser Pro
385 390 395 400

<210> 84
<211> 1785
<212> DNA
<213> Homo sapiens

<400> 84
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tttgctactt taaggaatag accaaaaagc acagtaaata cccactattt ctccatcgat 120
gaggagctgg tctatgaaaa tttctatgca gattttggac cgctgaactt ggcaatggtg 180
tacagatatt gctgcaaact aaacaagaaa ctaaaatcat acagtttgtc aagaaagaaa 240
atagtgcact acacctgttt tgaccaacgg aaaagagcaa atgcagcatt tttgataggt 300
gcctatgcag taatctattt aaagaagaca ccagaagaag cctacagagc actcctgtct 360
ggctcaaacc ccccctatct tccattcagg gatgcttcct ttggaaattg cacttacaat 420
ctcaccattc tcgactgttt gcagggaatc agaaagggat tacaacatgg atttttgac 480
tttgagacat ttgatgtgga tgaatatgaa cattatgagc gagttgaaaa tggtgacttc 540
aactggattg ttccaggaaa atttttagca tttagtggac cacatcctaa aagcaaaatt 600
gagaatggtt atcctcttca cgcccctgaa gcctactttc cttatttcaa aaagcataat 660
gtgactgcag ttgtgaggct aaacaaaaag atttatgagg caaagcgctt cacagacgct 720
ggcttcgagc actatgacct cttcttcata gatggcagca cacccagtga caacatcgtg 780
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catgctgaaa taattgcttg gattagaata tgccggccag gctctattat aggaccccag 960
cagcacttcc tggaagaaaa acaagcatcg ttgtgggtcc aaggagacat tttccgatcc 1020
aaactgaaaa atcgaccatc cagtgaagga agtattaata aaattctttc tggcctagat 1080
gatatgtcta ttggtggaaa tctttcaaaa acacaaaaca tggaacgatt tggagaggat 1140
aacttagaag atgatgatgt ggaaatgaaa aatggtataa cccagggaga caaactacgt 1200

gccttaaaaa gtcagagaca gccacgtacc tcaccatcct gtgcatttag gtcagatgat 1260
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aacagcaacg ggggcaacct gaacagcccc ccaggccccc acagcgccaa gacagaggag 1680
cacaccacca tcctccgacc ctcctacacc gggctttctt cttcttcagc gagattcctg 1740
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<210> 85
<211> 594
<212> PRT
<213> Homo sapiens

<400> 85
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20 25 30
Asn Thr His Tyr Phe Ser Ile Asp Glu Glu Leu Val Tyr Glu Asn Phe
35 40 45
Tyr Ala Asp Phe Gly Pro Leu Asn Leu Ala Met Val Tyr Arg Tyr Cys
50 55 60
Cys Lys Leu Asn Lys Lys Leu Lys Ser Tyr Ser Leu Ser Arg Lys Lys
65 70 75 80
Ile Val His Tyr Thr Cys Phe Asp Gln Arg Lys Arg Ala Asn Ala Ala
85 90 95
Phe Leu Ile Gly Ala Tyr Ala Val Ile Tyr Leu Lys Lys Thr Pro Glu
100 105 110
Glu Ala Tyr Arg Ala Leu Leu Ser Gly Ser Asn Pro Pro Tyr Leu Pro
115 120 125
Phe Arg Asp Ala Ser Phe Gly Asn Cys Thr Tyr Asn Leu Thr Ile Leu
130 135 140
Asp Cys Leu Gln Gly Ile Arg Lys Gly Leu Gln His Gly Phe Phe Asp
145 150 155 160
Phe Glu Thr Phe Asp Val Asp Glu Tyr Glu His Tyr Glu Arg Val Glu
165 170 175
Asn Gly Asp Phe Asn Trp Ile Val Pro Gly Lys Phe Leu Ala Phe Ser
180 185 190
Gly Pro His Pro Lys Ser Lys Ile Glu Asn Gly Tyr Pro Leu His Ala
195 200 205
Pro Glu Ala Tyr Phe Pro Tyr Phe Lys Lys His Asn Val Thr Ala Val
210 215 220
Val Arg Leu Asn Lys Lys Ile Tyr Glu Ala Lys Arg Phe Thr Asp Ala
225 230 235 240
Gly Phe Glu His Tyr Asp Leu Phe Phe Ile Asp Gly Ser Thr Pro Ser
245 250 255
Asp Asn Ile Val Arg Arg Phe Leu Asn Ile Cys Glu Asn Thr Glu Gly
260 265 270
Ala Ile Ala Val His Cys Lys Ala Gly Leu Gly Arg Thr Gly Thr Leu
275 280 285
Ile Ala Cys Tyr Val Met Lys His Tyr Arg Phe Thr His Ala Glu Ile
290 295 300
Ile Ala Trp Ile Arg Ile Cys Arg Pro Gly Ser Ile Ile Gly Pro Gln
305 310 315 320
Gln His Phe Leu Glu Glu Lys Gln Ala Ser Leu Trp Val Gln Gly Asp

325 330 335
Ile Phe Arg Ser Lys Leu Lys Asn Arg Pro Ser Ser Glu Gly Ser Ile
340 345 350
Asn Lys Ile Leu Ser Gly Leu Asp Asp Met Ser Ile Gly Gly Asn Leu
355 360 365
Ser Lys Thr Gln Asn Met Glu Arg Phe Gly Glu Asp Asn Leu Glu Asp
370 375 380
Asp Asp Val Glu Met Lys Asn Gly Ile Thr Gln Gly Asp Lys Leu Arg
385 390 395 400
Ala Leu Lys Ser Gln Arg Gln Pro Arg Thr Ser Pro Ser Cys Ala Phe
405 410 415
Arg Ser Asp Asp Thr Lys Gly His Pro Arg Ala Val Ser Gln Pro Phe
420 425 430
Arg Leu Ser Ser Ser Leu Gln Gly Ser Ala Val Thr Leu Lys Thr Ser
435 440 445
Lys Met Ala Leu Ser Pro Ser Ala Thr Ala Lys Arg Ile Asn Arg Thr
450 455 460
Ser Leu Ser Ser Gly Ala Thr Val Arg Ser Phe Ser Ile Asn Ser Arg
465 470 475 480
Leu Ala Ser Ser Leu Gly Asn Leu Asn Ala Ala Thr Asp Asp Pro Glu
485 490 495
Asn Lys Lys Thr Ser Ser Ser Ser Lys Ala Gly Phe Thr Ala Ser Pro
500 505 510
Phe Thr Asn Leu Leu Asn Gly Ser Ser Gln Pro Thr Thr Arg Asn Tyr
515 520 525
Pro Glu Leu Asn Asn Asn Gln Tyr Asn Arg Ser Ser Asn Ser Asn Gly
530 535 540
Gly Asn Leu Asn Ser Pro Pro Gly Pro His Ser Ala Lys Thr Glu Glu
545 550 555 560
His Thr Thr Ile Leu Arg Pro Ser Tyr Thr Gly Leu Ser Ser Ser Ser
565 570 575
Ala Arg Phe Leu Ser Arg Ser Ile Pro Ser Leu Gln Ser Glu Tyr Val
580 585 590
His Tyr

<210> 86
<211> 2438
<212> DNA
<213> Homo sapiens

<400> 86
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ctcgagtagc cacgggcgcg atcgggacca gaagtctcct cctccatgat cactttggaa 120
gccgggggaa gactttgccc tgccctgaga gctggtctgc gtttcccagg cgcggcggcg 180
gcggagcagc agctgcagca gccgagtcca aataggagcg gccacagcca ggggcgtgtg 240
cgccccgcgc ggagcgagct cgggttcccc tcggaatgtc cccggggcgc ccggcgcgct 300
gaccccgaag ccgcctccgc cttcggcgcc tgctgcctcc ctcggccagg cttgttgttc 360
gggactgtga gcttcctggc tcctgggcag tggggaagcc cccgggggcg agtgacctca 420
gctggccacg acccagccct cccccgtgcg tatctcgctt aagatggcag cggagtcagg 480
ggaactaatc ggggcttgtg agttcatgaa agatcggtta tattttgcta ctttaaggaa 540
tagaccaaaa agcacagtaa atacccacta tttctccatc gatgaggagc tggtctatga 600
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actaaacaag aaactaaaat catacagttt gtcaagaaag aaaatagtgc actacacctg 720
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cctgaacagc cccccaggcc cccacagcgc caagacagag gagcacacca ccatcctccg 2160
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ttcccagccg aggctgccac caaagaaatt taatagtgcc aaggaagcct tctgagcgat 2340
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aaacgccaag tcacaaaaaa aaaaaaaaaa aaaaaaaa 2438

<210> 87
<211> 623
<212> PRT
<213> Homo sapiens

<400> 87
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Asp Arg Leu Tyr Phe Ala Thr Leu Arg Asn Arg Pro Lys Ser Thr Val
20 25 30
Asn Thr His Tyr Phe Ser Ile Asp Glu Glu Leu Val Tyr Glu Asn Phe
35 40 45
Tyr Ala Asp Phe Gly Pro Leu Asn Leu Ala Met Val Tyr Arg Tyr Cys
50 55 60
Cys Lys Leu Asn Lys Lys Leu Lys Ser Tyr Ser Leu Ser Arg Lys Lys
65 70 75 80
Ile Val His Tyr Thr Cys Phe Asp Gln Arg Lys Arg Ala Asn Ala Ala
85 90 95
Phe Leu Ile Gly Ala Tyr Ala Val Ile Tyr Leu Lys Lys Thr Pro Glu
100 105 110
Glu Ala Tyr Arg Ala Leu Leu Ser Gly Ser Asn Pro Pro Tyr Leu Pro
115 120 125
Phe Arg Asp Ala Ser Phe Gly Asn Cys Thr Tyr Asn Leu Thr Ile Leu
130 135 140
Asp Cys Leu Gln Gly Ile Arg Lys Gly Leu Gln His Gly Phe Phe Asp
145 150 155 160
Phe Glu Thr Phe Asp Val Asp Glu Tyr Glu His Tyr Glu Arg Val Glu
165 170 175
Asn Gly Asp Phe Asn Trp Ile Val Pro Gly Lys Phe Leu Ala Phe Ser
180 185 190
Gly Pro His Pro Lys Ser Lys Ile Glu Asn Gly Tyr Pro Leu His Ala

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        195                 200                 205
Pro Glu Ala Tyr Phe Pro Tyr Phe Lys Lys His Asn Val Thr Ala Val
    210                 215                 220
Val Arg Leu Asn Lys Lys Ile Tyr Glu Ala Lys Arg Phe Thr Asp Ala
225                 230                 235                 240
Gly Phe Glu His Tyr Asp Leu Phe Phe Ile Asp Gly Ser Thr Pro Ser
                245                 250                 255
Asp Asn Ile Val Arg Arg Phe Leu Asn Ile Cys Glu Asn Thr Glu Gly
            260                 265                 270
Ala Ile Ala Val His Cys Lys Ala Gly Leu Gly Arg Thr Gly Thr Leu
        275                 280                 285
Ile Ala Cys Tyr Val Met Lys His Tyr Arg Phe Thr His Ala Glu Ile
    290                 295                 300
Ile Ala Trp Ile Arg Ile Cys Arg Pro Gly Ser Ile Ile Gly Pro Gln
305                 310                 315                 320
Gln His Phe Leu Glu Glu Lys Gln Ala Ser Leu Trp Val Gln Gly Asp
                325                 330                 335
Ile Phe Arg Ser Lys Leu Lys Asn Arg Pro Ser Ser Glu Gly Ser Ile
            340                 345                 350
Asn Lys Ile Leu Ser Gly Leu Asp Asp Met Ser Ile Gly Gly Asn Leu
        355                 360                 365
Ser Lys Thr Gln Asn Met Glu Arg Phe Gly Glu Asp Asn Leu Glu Asp
    370                 375                 380
Asp Asp Val Glu Met Lys Asn Gly Ile Thr Gln Gly Asp Lys Leu Arg
385                 390                 395                 400
Ala Leu Lys Ser Gln Arg Gln Pro Arg Thr Ser Pro Ser Cys Ala Phe
                405                 410                 415
Arg Ser Asp Asp Thr Lys Gly His Pro Arg Ala Val Ser Gln Pro Phe
            420                 425                 430
Arg Leu Ser Ser Ser Leu Gln Gly Ser Ala Val Thr Leu Lys Thr Ser
        435                 440                 445
Lys Met Ala Leu Ser Pro Ser Ala Thr Ala Lys Arg Ile Asn Arg Thr
    450                 455                 460
Ser Leu Ser Ser Gly Ala Thr Val Arg Ser Phe Ser Ile Asn Ser Arg
465                 470                 475                 480
Leu Ala Ser Ser Leu Gly Asn Leu Asn Ala Ala Thr Asp Asp Pro Glu
                485                 490                 495
Asn Lys Lys Thr Ser Ser Ser Ser Lys Ala Gly Phe Thr Ala Ser Pro
            500                 505                 510
Phe Thr Asn Leu Leu Asn Gly Ser Ser Gln Pro Thr Thr Arg Asn Tyr
        515                 520                 525
Pro Glu Leu Asn Asn Asn Gln Tyr Asn Arg Ser Ser Asn Ser Asn Gly
    530                 535                 540
Gly Asn Leu Asn Ser Pro Pro Gly Pro His Ser Ala Lys Thr Glu Glu
545                 550                 555                 560
His Thr Thr Ile Leu Arg Pro Ser Tyr Thr Gly Leu Ser Ser Ser Ser
                565                 570                 575
Ala Arg Phe Leu Ser Arg Ser Ile Pro Val Ser Ala Gln Thr Pro Pro
            580                 585                 590
Pro Gly Pro Gln Asn Pro Glu Cys Asn Phe Cys Ala Leu Pro Ser Gln
        595                 600                 605
Pro Arg Leu Pro Pro Lys Lys Phe Asn Ser Ala Lys Glu Ala Phe
    610                 615                 620
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<210> 88
<211> 1890
<212> DNA

<213> Homo sapiens

<400> 88
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ggagcgagct cgggttcccc tcggaatgtc cccggggcgc ccggcgcgct gaccccgaag 300
ccgcctccgc cttcggcgcc tgctgcctcc ctcggccagg cttgttgttc gggactgtga 360
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ggggcttgtg agttcatgaa agatcggtta tattttgcta ctttaaggaa tagaccaaaa 540
agcacagtaa atacccacta tttctccatc gatgaggagc tggtctatga aaatttctat 600
gcagattttg gaccgctgaa cttggcaatg gtgtacagat attgctgcaa actaaacaag 660
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cggaaaagag caaatgcagc atttttgata ggtgcctatg cagtaatcta tttaaagaag 780
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atcagaaagg gattacaaca tggatttttt gactttgaga catttgatgt ggatgaatat 960
gaacattatg agcgagttga aaatggtgac ttcaactgga ttgttccagg aaaatttta 1020
gcatttagtg gaccacatcc taaaagcaaa attgagaatg gttatcctct tcacgccct 1080
gaagcctact ttccttattt caaaaagcat aatgtgactg cagttgtgag gctaaacaaa 1140
aagatttatg aggcaaagcg cttcacagac gctggcttcg agcactatga cctcttcttc 1200
atagatggca gcacacccag tgacaacatc gtgcgaaggt tcctgaacat ctgtgagaac 1260
accgaagggg ccatcgccgt tcactgcaaa gctggtcttg gaagaacagg gacattgata 1320
gcctgttatg taatgaaaca ctacaggttt acacatgctg aaataattgc ttggattaga 1380
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tcgttgtggg tccaaggaga cattttccga tccaaactga aaaatcgacc atccagtgaa 1500
ggaagtatta ataaaattct ttctggccta gatgatatgt ctattggtgg aaatctttca 1560
aaaacacaaa acatggaacg atttggagag gtaagttttc cctaggagat tctatcttct 1620
taaaactgat gttctgcatt tgtttctcag ttggacctat ataacatagc agtgtctttt 1680
ctctggatgc cacgagtacc aagtttttag aagtagagcc atccgtctat atagcaagaa 1740
gcagaggaaa gaaaccaatt gcccttaaaa aaaaaaagct ataatttaag gagtaaatta 1800
taaaggaggc tactctggta aggggtaata tttatagaaa ggaaacagaa aagcaaactt 1860
tctatttgaa aaaaaaaaaa aaaaaaaaaa 1890

<210> 89
<211> 383
<212> PRT
<213> Homo sapiens

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Ile Val His Tyr Thr Cys Phe Asp Gln Arg Lys Arg Ala Asn Ala Ala
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Phe Leu Ile Gly Ala Tyr Ala Val Ile Tyr Leu Lys Lys Thr Pro Glu
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Glu Ala Tyr Arg Ala Leu Leu Ser Gly Ser Asn Pro Pro Tyr Leu Pro
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Gln His Phe Leu Glu Glu Lys Gln Ala Ser Leu Trp Val Gln Gly Asp
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Ile Phe Arg Ser Lys Leu Lys Asn Arg Pro Ser Ser Glu Gly Ser Ile
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Asn Lys Ile Leu Ser Gly Leu Asp Asp Met Ser Ile Gly Gly Asn Leu
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Tyr Leu Asp Ile Thr Asp Arg Leu Cys Phe Ala Ile Leu Tyr Ser Arg
50 55 60
Pro Lys Ser Ala Ser Asn Val His Tyr Phe Ser Ile Asp Asn Glu Leu
65 70 75 80
Glu Tyr Glu Asn Phe Tyr Ala Asp Phe Gly Pro Leu Asn Leu Ala Met
85 90 95
Val Tyr Arg Tyr Cys Cys Lys Ile Asn Lys Lys Leu Lys Ser Ile Thr
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130 135 140
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145 150 155 160
Ser Tyr Ile Pro Phe Arg Asp Ala Ala Tyr Gly Ser Cys Asn Phe Tyr
165 170 175
Ile Thr Leu Leu Asp Cys Phe His Ala Val Lys Lys Ala Met Gln Tyr
180 185 190
Gly Phe Leu Asn Phe Asn Ser Phe Asn Leu Asp Glu Tyr Glu His Tyr
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Glu Lys Ala Glu Asn Gly Asp Leu Asn Trp Ile Ile Pro Asp Arg Phe
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Ile Ala Phe Cys Gly Pro His Ser Arg Ala Arg Leu Glu Ser Gly Tyr
225 230 235 240
His Gln His Ser Pro Glu Thr Tyr Ile Gln Tyr Phe Lys Asn His Asn
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Val Thr Thr Ile Ile Arg Leu Asn Lys Arg Met Tyr Asp Ala Lys Arg
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275 280 285
Ser Thr Pro Thr Asp Ala Ile Val Lys Glu Phe Leu Asp Ile Cys Glu
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325 330 335
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Pro Lys Ser Ala Ser Asn Val His Tyr Phe Ser Ile Asp Asn Glu Leu
65                  70                  75                  80
Glu Tyr Glu Asn Phe Tyr Ala Asp Phe Gly Pro Leu Asn Leu Ala Met
                85                  90                  95
Val Tyr Arg Tyr Cys Cys Lys Ile Asn Lys Lys Leu Lys Ser Ile Thr
            100                 105                 110
Met Leu Arg Lys Lys Ile Val His Phe Thr Gly Ser Asp Gln Arg Lys
        115                 120                 125
Gln Ala Asn Ala Ala Phe Leu Val Gly Cys Tyr Met Val Ile Tyr Leu
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145                 150                 155                 160
Ser Tyr Ile Pro Phe Arg Asp Ala Ala Tyr Gly Ser Cys Asn Phe Tyr
                165                 170                 175
Ile Thr Leu Leu Asp Cys Phe His Ala Val Lys Lys Ala Met Gln Tyr
            180                 185                 190
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Glu Lys Ala Glu Asn Gly Asp Leu Asn Trp Ile Ile Pro Asp Arg Phe
    210                 215                 220
Ile Ala Phe Cys Gly Pro His Ser Arg Ala Arg Leu Glu Ser Gly Tyr
225                 230                 235                 240
His Gln His Ser Pro Glu Thr Tyr Ile Gln Tyr Phe Lys Asn His Asn
                245                 250                 255
Val Thr Thr Ile Ile Arg Leu Asn Lys Arg Met Tyr Asp Ala Lys Arg
            260                 265                 270
Phe Thr Asp Ala Gly Phe Asp His His Asp Leu Phe Phe Ala Asp Gly
        275                 280                 285
Ser Thr Pro Thr Asp Ala Ile Val Lys Glu Phe Leu Asp Ile Cys Glu
    290                 295                 300
Asn Ala Glu Gly Ala Ile Ala Val His Cys Lys Ala Gly Leu Gly Arg
305                 310                 315                 320
Thr Gly Thr Leu Ile Ala Cys Tyr Ile Met Lys His Tyr Arg Met Thr
                325                 330                 335
Ala Ala Glu Thr Ile Ala Trp Val Arg Ile Cys Arg Pro Gly Ser Val
            340                 345                 350
Ile Gly Pro Gln Gln Gln Phe Leu Val Met Lys Gln Thr Asn Leu Trp
        355                 360                 365
Leu Glu Gly Asp Tyr Phe Arg Gln Lys Leu Lys Gly Gln Glu Asn Gly
    370                 375                 380
Gln His Arg Ala Ala Phe Ser Lys Leu Leu Ser Gly Val Asp Asp Ile
385                 390                 395                 400
Ser Ile Asn Gly Val Glu Asn Gln Asp Gln Gln Glu Pro Glu Pro Tyr
                405                 410                 415
Ser Asp Asp Asp Glu Ile Asn Gly Val Thr Gln Gly Asp Arg Leu Arg
            420                 425                 430
Ala Leu Lys Ser Arg Arg Gln Ser Lys Thr Asn Ala Ile Pro Leu Thr
        435                 440                 445
Asp Gly Trp Leu Ser Gln Ala Val Thr Phe Leu Asp Arg Leu Leu Ile
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Trp Leu Gly Ile His Lys Asp
465                 470
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<210> 94
<211> 834
<212> DNA
<213> Homo sapiens

<400> 94
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<210> 95
<211> 188
<212> PRT
<213> Homo sapiens

<400> 95
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20 25 30
Val Ala Ala Asn Asn Lys Leu Met Leu Ser Ser Asn Gln Ile Thr Met
35 40 45
Val Ile Asn Val Ser Val Glu Val Val Asn Thr Leu Tyr Glu Asp Ile
50 55 60
Gln Tyr Met Gln Val Pro Val Ala Asp Ser Pro Asn Ser Arg Leu Cys
65 70 75 80
Asp Phe Phe Asp Pro Ile Ala Asp His Ile His Ser Val Glu Met Lys
85 90 95
Gln Gly Arg Thr Leu Leu His Cys Ala Ala Gly Val Ser Arg Ser Ala
100 105 110
Ala Leu Cys Leu Ala Tyr Leu Met Lys Tyr His Ala Met Ser Leu Leu
115 120 125
Asp Ala His Thr Trp Thr Lys Ser Cys Arg Pro Ile Ile Arg Pro Asn
130 135 140
Ser Gly Phe Trp Glu Gln Leu Ile His Tyr Glu Phe Gln Leu Phe Gly
145 150 155 160
Lys Asn Thr Val His Met Val Ser Ser Pro Val Gly Met Ile Pro Asp
165 170 175
Ile Tyr Glu Lys Glu Val Arg Leu Met Ile Pro Leu
180 185

<210> 96
<211> 926
<212> DNA
<213> Homo sapiens

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<211> 184
<212> PRT
<213> Homo sapiens

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His Ile Leu Ser Val His Asp Ser Ala Arg Pro Met Leu Glu Gly Val
35 40 45
Lys Tyr Leu Cys Ile Pro Ala Ala Asp Ser Pro Ser Gln Asn Leu Thr
50 55 60
Arg His Phe Lys Glu Ser Ile Lys Phe Ile His Glu Cys Arg Leu Arg
65 70 75 80
Gly Glu Ser Cys Leu Val His Cys Leu Ala Gly Val Ser Arg Ser Val
85 90 95
Thr Leu Val Ile Ala Tyr Ile Met Thr Val Thr Asp Phe Gly Trp Glu
100 105 110
Asp Ala Leu His Thr Val Arg Ala Gly Arg Ser Cys Ala Asn Pro Asn
115 120 125
Val Gly Phe Gln Arg Gln Leu Gln Glu Phe Glu Lys His Glu Val His
130 135 140
Gln Tyr Arg Gln Trp Leu Lys Glu Glu Tyr Gly Glu Ser Pro Leu Gln
145 150 155 160
Asp Ala Glu Glu Ala Lys Asn Ile Leu Ala Ala Pro Gly Ile Leu Lys
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Phe Trp Ala Phe Leu Arg Arg Leu
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<210> 98
<211> 4882
<212> DNA
<213> Homo sapiens

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<210> 99
<211> 1256
<212> PRT
<213> Homo sapiens

<400> 99

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            20                  25                  30
Leu Thr Thr Ala Lys Met Pro Ser Val Pro Leu Ser Ser Asp Pro Leu
        35                  40                  45
Pro Thr His Thr Thr Ala Phe Ser Pro Ala Ser Thr Phe Glu Arg Glu
    50                  55                  60
Asn Asp Phe Ser Glu Thr Thr Thr Ser Leu Ser Pro Asp Asn Thr Ser
65                  70                  75                  80
Thr Gln Val Ser Pro Asp Ser Leu Asp Asn Ala Ser Ala Phe Asn Thr
                85                  90                  95
Thr Gly Val Ser Ser Val Gln Thr Pro His Leu Pro Thr His Ala Asp
            100                 105                 110
Ser Gln Thr Pro Ser Ala Gly Thr Asp Thr Gln Thr Phe Ser Gly Ser
        115                 120                 125
Ala Ala Asn Ala Lys Leu Asn Pro Thr Pro Gly Ser Asn Ala Ile Ser
    130                 135                 140
Asp Ala Tyr Leu Asn Ala Ser Glu Thr Thr Thr Leu Ser Pro Ser Gly
145                 150                 155                 160
Ser Ala Val Ile Ser Thr Thr Thr Ile Ala Thr Thr Pro Ser Lys Pro
                165                 170                 175
Thr Cys Asp Glu Lys Tyr Ala Asn Ile Thr Val Asp Tyr Leu Tyr Asn
            180                 185                 190
Lys Glu Thr Lys Leu Phe Thr Ala Lys Leu Asn Val Asn Glu Asn Val
        195                 200                 205
Glu Cys Gly Asn Asn Thr Cys Thr Asn Asn Glu Val His Asn Leu Thr
    210                 215                 220
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Glu Cys Lys Asn Ala Ser Val Ser Ile Ser His Asn Ser Cys Thr Ala
225 230 235 240
Pro Asp Lys Thr Leu Ile Leu Asp Val Pro Pro Gly Val Glu Lys Phe
245 250 255
Gln Leu His Asp Cys Thr Gln Val Glu Lys Ala Asp Thr Thr Ile Cys
260 265 270
Leu Lys Trp Lys Asn Ile Glu Thr Phe Thr Cys Asp Thr Gln Asn Ile
275 280 285
Thr Tyr Arg Phe Gln Cys Gly Asn Met Ile Phe Asp Asn Lys Glu Ile
290 295 300
Lys Leu Glu Asn Leu Glu Pro Glu His Glu Tyr Lys Cys Asp Ser Glu
305 310 315 320
Ile Leu Tyr Asn Asn His Lys Phe Thr Asn Ala Ser Lys Ile Ile Lys
325 330 335
Thr Asp Phe Gly Ser Pro Gly Glu Pro Gln Ile Ile Phe Cys Arg Ser
340 345 350
Glu Ala Ala His Gln Gly Val Ile Thr Trp Asn Pro Pro Gln Arg Ser
355 360 365
Phe His Asn Phe Thr Leu Cys Tyr Ile Lys Glu Thr Glu Lys Asp Cys
370 375 380
Leu Asn Leu Asp Lys Asn Leu Ile Lys Tyr Asp Leu Gln Asn Leu Lys
385 390 395 400
Pro Tyr Thr Lys Tyr Val Leu Ser Leu His Ala Tyr Ile Ile Ala Lys
405 410 415
Val Gln Arg Asn Gly Ser Ala Ala Met Cys His Phe Thr Thr Lys Ser
420 425 430
Ala Pro Pro Ser Gln Val Trp Asn Met Thr Val Ser Met Thr Ser Asp
435 440 445
Asn Ser Met His Val Lys Cys Arg Pro Pro Arg Asp Arg Asn Gly Pro
450 455 460
His Glu Arg Tyr His Leu Glu Val Glu Ala Gly Asn Thr Leu Val Arg
465 470 475 480
Asn Glu Ser His Lys Asn Cys Asp Phe Arg Val Lys Asp Leu Gln Tyr
485 490 495
Ser Thr Asp Tyr Thr Phe Lys Ala Tyr Phe His Asn Gly Asp Tyr Pro
500 505 510
Gly Glu Pro Phe Ile Leu His His Ser Thr Ser Tyr Asn Ser Lys Ala
515 520 525
Leu Ile Ala Phe Leu Ala Phe Leu Ile Ile Val Thr Ser Ile Ala Leu
530 535 540
Leu Val Val Leu Tyr Lys Ile Tyr Asp Leu His Lys Lys Arg Ser Cys
545 550 555 560
Asn Leu Asp Glu Gln Gln Glu Leu Val Glu Arg Asp Asp Glu Lys Gln
565 570 575
Leu Met Asn Val Glu Pro Ile His Ala Asp Ile Leu Leu Glu Thr Tyr
580 585 590
Lys Arg Lys Ile Ala Asp Glu Gly Arg Leu Phe Leu Ala Glu Phe Gln
595 600 605
Ser Ile Pro Arg Val Phe Ser Lys Phe Pro Ile Lys Glu Ala Arg Lys
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Pro Phe Asn Gln Asn Lys Asn Arg Tyr Val Asp Ile Leu Pro Tyr Asp
625 630 635 640
Tyr Asn Arg Val Glu Leu Ser Glu Ile Asn Gly Asp Ala Gly Ser Asn
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Tyr Ile Asn Ala Ser Tyr Ile Asp Gly Phe Lys Glu Pro Arg Lys Tyr
660 665 670
Ile Ala Ala Gln Gly Pro Arg Asp Glu Thr Val Asp Asp Phe Trp Arg
675 680 685

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Met Ile Trp Glu Gln Lys Ala Thr Val Ile Val Met Val Thr Arg Cys
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Glu Glu Gly Asn Arg Asn Lys Cys Ala Glu Tyr Trp Pro Ser Met Glu
705                 710                 715                 720
Glu Gly Thr Arg Ala Phe Gly Asp Val Val Val Lys Ile Asn Gln His
                725                 730                 735
Lys Arg Cys Pro Asp Tyr Ile Ile Gln Lys Leu Asn Ile Val Asn Lys
            740                 745                 750
Lys Glu Lys Ala Thr Gly Arg Glu Val Thr His Ile Gln Phe Thr Ser
        755                 760                 765
Trp Pro Asp His Gly Val Pro Glu Asp Pro His Leu Leu Leu Lys Leu
    770                 775                 780
Arg Arg Arg Val Asn Ala Phe Ser Asn Phe Phe Ser Gly Pro Ile Val
785                 790                 795                 800
Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Tyr Ile Gly Ile
                805                 810                 815
Asp Ala Met Leu Glu Gly Leu Glu Ala Glu Asn Lys Val Asp Val Tyr
            820                 825                 830
Gly Tyr Val Val Lys Leu Arg Arg Gln Arg Cys Leu Met Val Gln Val
        835                 840                 845
Glu Ala Gln Tyr Ile Leu Ile His Gln Ala Leu Val Glu Tyr Asn Gln
    850                 855                 860
Phe Gly Glu Thr Glu Val Asn Leu Ser Glu Leu His Pro Tyr Leu His
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Asn Met Lys Lys Arg Asp Pro Pro Ser Glu Pro Ser Pro Leu Glu Ala
                885                 890                 895
Glu Phe Gln Arg Leu Pro Ser Tyr Arg Ser Trp Arg Thr Gln His Ile
            900                 905                 910
Gly Asn Gln Glu Glu Asn Lys Ser Lys Asn Arg Asn Ser Asn Val Ile
        915                 920                 925
Pro Tyr Asp Tyr Asn Arg Val Pro Leu Lys His Glu Leu Glu Met Ser
    930                 935                 940
Lys Glu Ser Glu His Asp Ser Asp Glu Ser Ser Asp Asp Asp Ser Asp
945                 950                 955                 960
Ser Glu Glu Pro Ser Lys Tyr Ile Asn Ala Ser Phe Ile Met Ser Tyr
                965                 970                 975
Trp Lys Pro Glu Val Met Ile Ala Ala Gln Gly Pro Leu Lys Glu Thr
            980                 985                 990
Ile Gly Asp Phe Trp Gln Met Ile Phe Gln Arg Lys Val Lys Val Ile
        995                 1000                1005
Val Met Leu Thr Glu Leu Lys His Gly Asp Gln Glu Ile Cys Ala Gln
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Tyr Trp Gly Glu Gly Lys Gln Thr Tyr Gly Asp Ile Glu Val Asp Leu
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Lys Asp Thr Asp Lys Ser Ser Thr Tyr Thr Leu Arg Val Phe Glu Leu
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Arg His Ser Lys Arg Lys Asp Ser Arg Thr Val Tyr Gln Tyr Gln Tyr
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Thr Asn Trp Ser Val Glu Gln Leu Pro Ala Glu Pro Lys Glu Leu Ile
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Ser Met Ile Gln Val Val Lys Gln Lys Leu Pro Gln Lys Asn Ser Ser
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Glu Gly Asn Lys His His Lys Ser Thr Pro Leu Leu Ile His Cys Arg
1105                1110                1115                1120
Asp Gly Ser Gln Gln Thr Gly Ile Phe Cys Ala Leu Leu Asn Leu Leu
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Glu Ser Ala Glu Thr Glu Glu Val Val Asp Ile Phe Gln Val Val Lys
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Gln Phe Leu Tyr Asp Val Ile Ala Ser Thr Tyr Pro Ala Gln Asn Gly
1170 1175 1180
Gln Val Lys Lys Asn Asn His Gln Glu Asp Lys Ile Glu Phe Asp Asn
1185 1190 1195 1200
Glu Val Asp Lys Val Lys Gln Asp Ala Asn Cys Val Asn Pro Leu Gly
1205 1210 1215
Ala Pro Glu Lys Leu Pro Glu Ala Lys Glu Gln Ala Glu Gly Ser Glu
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<210> 100
<211> 4543
<212> DNA
<213> Homo sapiens

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Ala Val Ile Ser Thr Thr Thr Ile Ala Thr Thr Pro Ser Lys Pro Thr
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Lys Trp Lys Asn Ile Glu Thr Phe Thr Cys Asp Thr Gln Asn Ile Thr
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Tyr Arg Phe Gln Cys Gly Asn Met Ile Phe Asp Asn Lys Glu Ile Lys
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Leu Glu Asn Leu Glu Pro Glu His Glu Tyr Lys Cys Asp Ser Glu Ile
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Leu Tyr Asn Asn His Lys Phe Thr Asn Ala Ser Lys Ile Ile Lys Thr
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Asp Phe Gly Ser Pro Gly Glu Pro Gln Ile Ile Phe Cys Arg Ser Glu
225                 230                 235                 240
Ala Ala His Gln Gly Val Ile Thr Trp Asn Pro Pro Gln Arg Ser Phe
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His Asn Phe Thr Leu Cys Tyr Ile Lys Glu Thr Glu Lys Asp Cys Leu
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Asn Leu Asp Lys Asn Leu Ile Lys Tyr Asp Leu Gln Asn Leu Lys Pro
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Tyr Thr Lys Tyr Val Leu Ser Leu His Ala Tyr Ile Ile Ala Lys Val
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Gln Arg Asn Gly Ser Ala Ala Met Cys His Phe Thr Thr Lys Ser Ala
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Pro Pro Ser Gln Val Trp Asn Met Thr Val Ser Met Thr Ser Asp Asn
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Ser Met His Val Lys Cys Arg Pro Pro Arg Asp Arg Asn Gly Pro His
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Glu Arg Tyr His Leu Glu Val Glu Ala Gly Asn Thr Leu Val Arg Asn
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Glu Ser His Lys Asn Cys Asp Phe Arg Val Lys Asp Leu Gln Tyr Ser
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Glu Pro Phe Ile Leu His His Ser Thr Ser Tyr Asn Ser Lys Ala Leu
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Ile Ala Phe Leu Ala Phe Leu Ile Ile Val Thr Ser Ile Ala Leu Leu
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Val Val Leu Tyr Lys Ile Tyr Asp Leu His Lys Lys Arg Ser Cys Asn
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Leu Asp Glu Gln Gln Glu Leu Val Glu Arg Asp Asp Glu Lys Gln Leu
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Pro Asp His Gly Val Pro Glu Asp Pro His Leu Leu Leu Lys Leu Arg
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675 680 685
His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Tyr Ile Gly Ile Asp
690 695 700
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Tyr Val Val Lys Leu Arg Arg Gln Arg Cys Leu Met Val Gln Val Glu
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835 840 845
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850 855 860
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965 970 975
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<400> 102

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<213> Homo sapiens

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Ser Gln Thr Pro Ser Ala Gly Thr Asp Thr Gln Thr Phe Ser Gly Ser
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Val Ser Pro Leu Thr Thr Thr Leu Ser Leu Ala His His Ser Ser Ala
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Asp Ala Tyr Leu Asn Ala Ser Glu Thr Thr Thr Leu Ser Pro Ser Gly
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His Glu Arg Tyr His Leu Glu Val Glu Ala Gly Asn Thr Leu Val Arg
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Ser Thr Asp Tyr Thr Phe Lys Ala Tyr Phe His Asn Gly Asp Tyr Pro
545                 550                 555                 560
Gly Glu Pro Phe Ile Leu His His Ser Thr Ser Tyr Asn Ser Lys Ala
                565                 570                 575
Leu Ile Ala Phe Leu Ala Phe Leu Ile Ile Val Thr Ser Ile Ala Leu
            580                 585                 590
Leu Val Val Leu Tyr Lys Ile Tyr Asp Leu His Lys Lys Arg Ser Cys
        595                 600                 605
Asn Leu Asp Glu Gln Gln Glu Leu Val Glu Arg Asp Asp Glu Lys Gln
    610                 615                 620
Leu Met Asn Val Glu Pro Ile His Ala Asp Ile Leu Leu Glu Thr Tyr
625                 630                 635                 640
Lys Arg Lys Ile Ala Asp Glu Gly Arg Leu Phe Leu Ala Glu Phe Gln
                645                 650                 655
Ser Ile Pro Arg Val Phe Ser Lys Phe Pro Ile Lys Glu Ala Arg Lys
            660                 665                 670
Pro Phe Asn Gln Asn Lys Asn Arg Tyr Val Asp Ile Leu Pro Tyr Asp
        675                 680                 685
Tyr Asn Arg Val Glu Leu Ser Glu Ile Asn Gly Asp Ala Gly Ser Asn
    690                 695                 700
Tyr Ile Asn Ala Ser Tyr Ile Asp Gly Phe Lys Glu Pro Arg Lys Tyr
705                 710                 715                 720
Ile Ala Ala Gln Gly Pro Arg Asp Glu Thr Val Asp Asp Phe Trp Arg
                725                 730                 735
Met Ile Trp Glu Gln Lys Ala Thr Val Ile Val Met Val Thr Arg Cys
            740                 745                 750
Glu Glu Gly Asn Arg Asn Lys Cys Ala Glu Tyr Trp Pro Ser Met Glu
        755                 760                 765
Glu Gly Thr Arg Ala Phe Gly Asp Val Val Val Lys Ile Asn Gln His
    770                 775                 780
Lys Arg Cys Pro Asp Tyr Ile Ile Gln Lys Leu Asn Ile Val Asn Lys
785                 790                 795                 800
Lys Glu Lys Ala Thr Gly Arg Glu Val Thr His Ile Gln Phe Thr Ser
                805                 810                 815
Trp Pro Asp His Gly Val Pro Glu Asp Pro His Leu Leu Leu Lys Leu
            820                 825                 830
Arg Arg Arg Val Asn Ala Phe Ser Asn Phe Phe Ser Gly Pro Ile Val
        835                 840                 845
Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Tyr Ile Gly Ile
    850                 855                 860
Asp Ala Met Leu Glu Gly Leu Glu Ala Glu Asn Lys Val Asp Val Tyr
865                 870                 875                 880
Gly Tyr Val Val Lys Leu Arg Arg Gln Arg Cys Leu Met Val Gln Val
                885                 890                 895
Glu Ala Gln Tyr Ile Leu Ile His Gln Ala Leu Val Glu Tyr Asn Gln
            900                 905                 910
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Phe Gly Glu Thr Glu Val Asn Leu Ser Glu Leu His Pro Tyr Leu His
915 920 925
Asn Met Lys Lys Arg Asp Pro Pro Ser Glu Pro Ser Pro Leu Glu Ala
930 935 940
Glu Phe Gln Arg Leu Pro Ser Tyr Arg Ser Trp Arg Thr Gln His Ile
945 950 955 960
Gly Asn Gln Glu Glu Asn Lys Ser Lys Asn Arg Asn Ser Asn Val Ile
965 970 975
Pro Tyr Asp Tyr Asn Arg Val Pro Leu Lys His Glu Leu Glu Met Ser
980 985 990
Lys Glu Ser Glu His Asp Ser Asp Glu Ser Ser Asp Asp Asp Ser Asp
995 1000 1005
Ser Glu Glu Pro Ser Lys Tyr Ile Asn Ala Ser Phe Ile Met Ser Tyr
1010 1015 1020
Trp Lys Pro Glu Val Met Ile Ala Ala Gln Gly Pro Leu Lys Glu Thr
1025 1030 1035 1040
Ile Gly Asp Phe Trp Gln Met Ile Phe Gln Arg Lys Val Lys Val Ile
1045 1050 1055
Val Met Leu Thr Glu Leu Lys His Gly Asp Gln Glu Ile Cys Ala Gln
1060 1065 1070
Tyr Trp Gly Glu Gly Lys Gln Thr Tyr Gly Asp Ile Glu Val Asp Leu
1075 1080 1085
Lys Asp Thr Asp Lys Ser Ser Thr Tyr Thr Leu Arg Val Phe Glu Leu
1090 1095 1100
Arg His Ser Lys Arg Lys Asp Ser Arg Thr Val Tyr Gln Tyr Gln Tyr
1105 1110 1115 1120
Thr Asn Trp Ser Val Glu Gln Leu Pro Ala Glu Pro Lys Glu Leu Ile
1125 1130 1135
Ser Met Ile Gln Val Val Lys Gln Lys Leu Pro Gln Lys Asn Ser Ser
1140 1145 1150
Glu Gly Asn Lys His His Lys Ser Thr Pro Leu Leu Ile His Cys Arg
1155 1160 1165
Asp Gly Ser Gln Gln Thr Gly Ile Phe Cys Ala Leu Leu Asn Leu Leu
1170 1175 1180
Glu Ser Ala Glu Thr Glu Glu Val Val Asp Ile Phe Gln Val Val Lys
1185 1190 1195 1200
Ala Leu Arg Lys Ala Arg Pro Gly Met Val Ser Thr Phe Glu Gln Tyr
1205 1210 1215
Gln Phe Leu Tyr Asp Val Ile Ala Ser Thr Tyr Pro Ala Gln Asn Gly
1220 1225 1230
Gln Val Lys Lys Asn Asn His Gln Glu Asp Lys Ile Glu Phe Asp Asn
1235 1240 1245
Glu Val Asp Lys Val Lys Gln Asp Ala Asn Cys Val Asn Pro Leu Gly
1250 1255 1260
Ala Pro Glu Lys Leu Pro Glu Ala Lys Glu Gln Ala Glu Gly Ser Glu
1265 1270 1275 1280
Pro Thr Ser Gly Thr Glu Gly Pro Glu His Ser Val Asn Gly Pro Ala
1285 1290 1295
Ser Pro Ala Leu Asn Gln Gly Ser
1300

<210> 104
<211> 1045
<212> DNA
<213> Homo sapiens

<400> 104

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ttggctttgc ctttctggac acagaagtat ttgtgacagg gcaaagccca acaccttccc 180
ccactggtaa gaattaatat ttatattttt actaatttta ttttcttgtt gcaaagttta 240
tatatttaac tacaattttc tattattaac actgaaatta tttttaagga taaattttat 300
aatcatgagt gattcttgac attcacttgt tcttaaactt tctgcttata cgttatagag 360
tttaataact acctaaacat gttattaaat ttgtatatat attttgtgta taaatagtaa 420
cttttcccaa acttgacagt aaatcacaca acaggtttct actctctttt aatattttaa 480
gactataaaa aaatgcattt aaattagata acaaaatttt atagtctgaa agcaggttaa 540
cagctgtcta tgtatgttat agatatgtag ataacagatt tgcatatgtc tatatttctt 600
taagagtatg ttgctttttt cagtggtatg caaaaccttt gagactattg agatattttt 660
aaataataat tttcaaattc tactgaacac ttcaatagtc cttataaatg tcttaatcat 720
gagataaatt taaaacacag agatgctgca aataaattca tacatagtac atacaaaata 780
agagaaaaaa ttaaattgca gatggttaaa tatcacatca cttaactgat gttactgaaa 840
atgtattttc ctgcataatc atatggttga cagtatgcat taagaaggta agtaaaacaa 900
tgaagacaat tttgatttaa tatggtaatg cacaattcca actaacgtac attcaacaga 960
tcatgaaatt gggttattaa aatgaatatt tttgtcatta aataaaaatt ccgtccaaaa 1020
aaaaaaaaaa aaaaaaaaaa aaaaa 1045

<210> 105
<211> 34
<212> PRT
<213> Homo sapiens

<400> 105
Met Tyr Leu Trp Leu Lys Leu Leu Ala Phe Gly Phe Ala Phe Leu Asp
1 5 10 15
Thr Glu Val Phe Val Thr Gly Gln Ser Pro Thr Pro Ser Pro Thr Gly
20 25 30
Lys Asn

<210> 106
<211> 11
<212> PRT
<213> Unknown

<220>
<223> Conserved amino acids that may be found at
positions in a PTP polypeptide

<221> VARIANT
<222> 1
<223> Xaa = Ile or Val

<221> VARIANT
<222> 4, 7, 8
<223> Xaa = Any Amino Acid

<221> VARIANT
<222> 10
<223> Xaa = Ser or Thr

<400> 106
Xaa His Cys Xaa Ala Gly Xaa Xaa Arg Xaa Gly
1 5 10

<210> 107
<211> 8
<212> PRT
<213> Unknown

<220>
<223> Catalytic cysteine motif

<221> VARIANT
<222> 2, 3, 4, 5, 6
<223> Xaa = Any Amino Acid

<221> VARIANT
<222> 8
<223> Xaa = Ser or Thr

<400> 107
Cys Xaa Xaa Xaa Xaa Xaa Arg Xaa
1 5

<210> 108
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acids 1170-1176 of the EGF receptor sequence (fluorescently-labeled) may be substrates for acalytically active PTPs.

<400> 108
Asn Ala Glu Tyr Leu Arg Val
1 5

<210> 109
<211> 7
<212> PRT
<213> Unknown

<220>
<223> Catalytic cysteine motif sequence

<221> VARIANT
<222> 3, 4, 5, 6
<223> Xaa = Any Amino Acid

<400> 109
Cys Ser Xaa Xaa Xaa Xaa Arg
1 5

<210> 110
<211> 435
<212> PRT
<213> Unknown

<220>
<223> PTP1B mutant sequence

<400> 110
Met Glu Met Glu Lys Glu Phe Glu Gln Ile Asp Lys Ser Gly Ser Trp
1 5 10 15
Ala Ala Ile Tyr Gln Asp Ile Arg His Glu Ala Ser Asp Phe Pro Cys
20 25 30
Arg Val Ala Lys Leu Pro Lys Asn Lys Asn Arg Asn Arg Tyr Arg Asp
35 40 45
Val Ser Pro Phe Asp His Ser Arg Ile Lys Leu His Gln Glu Asp Asn
50 55 60
Asp Tyr Ile Asn Ala Ser Leu Ile Lys Met Glu Glu Ala Gln Arg Ser
65 70 75 80
Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Gly His Phe Trp
85 90 95
Glu Met Val Trp Glu Gln Lys Ser Arg Gly Val Val Met Leu Asn Arg
100 105 110
Val Met Glu Lys Gly Ser Leu Lys Cys Ala Gln Tyr Trp Pro Gln Lys
115 120 125
Glu Glu Lys Glu Met Ile Phe Glu Asp Thr Asn Leu Lys Leu Thr Leu
130 135 140
Ile Ser Glu Asp Ile Lys Ser Tyr Tyr Thr Val Arg Gln Leu Glu Leu
145 150 155 160
Glu Asn Leu Thr Thr Gln Glu Thr Arg Glu Ile Leu His Phe His Tyr
165 170 175
Thr Thr Trp Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe Leu
180 185 190
Asn Phe Leu Phe Lys Val Arg Glu Ser Gly Ser Leu Ser Pro Glu His
195 200 205
Gly Pro Val Val Val His Ala Ala Ala Gly Ile Gly Arg Ser Gly Thr
210 215 220
Phe Cys Leu Ala Asp Thr Cys Leu Leu Leu Met Asp Lys Arg Lys Asp
225 230 235 240
Pro Ser Ser Val Asp Ile Lys Lys Val Leu Leu Glu Met Arg Lys Phe
245 250 255
Arg Met Gly Leu Ile Gln Thr Ala Asp Gln Leu Arg Phe Ser Tyr Leu
260 265 270
Ala Val Ile Glu Gly Ala Lys Phe Ile Met Gly Asp Ser Ser Val Gln
275 280 285
Asp Gln Trp Lys Glu Leu Ser His Glu Asp Leu Glu Pro Pro Pro Glu
290 295 300
His Ile Pro Pro Pro Pro Arg Pro Pro Lys Arg Ile Leu Glu Pro His
305 310 315 320
Asn Gly Lys Cys Arg Glu Phe Phe Pro Asn His Gln Trp Val Lys Glu
325 330 335
Glu Thr Gln Glu Asp Lys Asp Cys Pro Ile Lys Glu Glu Lys Gly Ser
340 345 350
Pro Leu Asn Ala Ala Pro Tyr Gly Ile Glu Ser Met Ser Gln Asp Thr
355 360 365
Glu Val Arg Ser Arg Val Val Gly Gly Ser Leu Arg Gly Ala Gln Ala
370 375 380
Ala Ser Pro Ala Lys Gly Glu Pro Ser Leu Pro Glu Lys Asp Glu Asp
385 390 395 400
His Ala Leu Ser Tyr Trp Lys Pro Phe Leu Val Asn Met Cys Val Ala
405 410 415
Thr Val Leu Thr Ala Gly Ala Tyr Leu Cys Tyr Arg Phe Leu Phe Asn

420 425 430
Ser Asn Thr
435

<210> 111
<211> 435
<212> PRT
<213> unknown

<220>
<223> PTP1B mutant sequence

<400> 111
Met Glu Met Glu Lys Glu Phe Glu Gln Ile Asp Lys Ser Gly Ser Trp
1 5 10 15
Ala Ala Ile Tyr Gln Asp Ile Arg His Glu Ala Ser Asp Phe Pro Cys
20 25 30
Arg Val Ala Lys Leu Pro Lys Asn Lys Asn Arg Asn Arg Tyr Arg Asp
35 40 45
Val Ser Pro Phe Asp His Ser Arg Ile Lys Leu His Gln Glu Asp Asn
50 55 60
Asp Tyr Ile Asn Ala Ser Leu Ile Lys Met Glu Glu Ala Gln Arg Ser
65 70 75 80
Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Gly His Phe Trp
85 90 95
Glu Met Val Trp Glu Gln Lys Ser Arg Gly Val Val Met Leu Asn Arg
100 105 110
Val Met Glu Lys Gly Ser Leu Lys Cys Ala Gln Tyr Trp Pro Gln Lys
115 120 125
Glu Glu Lys Glu Met Ile Phe Glu Asp Thr Asn Leu Lys Leu Thr Leu
130 135 140
Ile Ser Glu Asp Ile Lys Ser Tyr Tyr Thr Val Arg Gln Leu Glu Leu
145 150 155 160
Glu Asn Leu Thr Thr Gln Glu Thr Arg Glu Ile Leu His Phe His Tyr
165 170 175
Thr Thr Trp Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe Leu
180 185 190
Asn Phe Leu Phe Lys Val Arg Glu Ser Gly Ser Leu Ser Pro Glu His
195 200 205
Gly Pro Val Val Val His Ser Ala Ala Gly Ile Gly Arg Ser Gly Thr
210 215 220
Phe Cys Leu Ala Asp Thr Cys Leu Leu Leu Met Asp Lys Arg Lys Asp
225 230 235 240
Pro Ser Ser Val Asp Ile Lys Lys Val Leu Leu Glu Met Arg Lys Phe
245 250 255
Arg Met Gly Leu Ile Gln Thr Ala Asp Gln Leu Arg Phe Ser Tyr Leu
260 265 270
Ala Val Ile Glu Gly Ala Lys Phe Ile Met Gly Asp Ser Ser Val Gln
275 280 285
Asp Gln Trp Lys Glu Leu Ser His Glu Asp Leu Glu Pro Pro Pro Glu
290 295 300
His Ile Pro Pro Pro Pro Arg Pro Pro Lys Arg Ile Leu Glu Pro His
305 310 315 320
Asn Gly Lys Cys Arg Glu Phe Phe Pro Asn His Gln Trp Val Lys Glu
325 330 335
Glu Thr Gln Glu Asp Lys Asp Cys Pro Ile Lys Glu Glu Lys Gly Ser
340 345 350

```
Pro Leu Asn Ala Ala Pro Tyr Gly Ile Glu Ser Met Ser Gln Asp Thr
        355                 360                 365
Glu Val Arg Ser Arg Val Val Gly Gly Ser Leu Arg Gly Ala Gln Ala
    370                 375                 380
Ala Ser Pro Ala Lys Gly Glu Pro Ser Leu Pro Glu Lys Asp Glu Asp
385                 390                 395                 400
His Ala Leu Ser Tyr Trp Lys Pro Phe Leu Val Asn Met Cys Val Ala
                405                 410                 415
Thr Val Leu Thr Ala Gly Ala Tyr Leu Cys Tyr Arg Phe Leu Phe Asn
            420                 425                 430
Ser Asn Thr
        435
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<210> 112
<211> 1087
<212> DNA
<213> Homo sapiens

<400> 112

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cggttacctg gatgggcgaa cacctctgag gctggctttg ttacctgggc aataagggac 120
tagcagttca gccgttttct atgcctgctg gatttgtttg tatttgttcc cagccactgc 180
tcatgtaatg tactccctta accaggaaat taaagcattc tcccggaata atctcaggaa 240
gcaatgcacc agggtgacaa cgctaactgg aaagaaaatt atagaaacat ggaaagatgc 300
cagaattcat gttgtggaag aagtagagcc gagcagtggg ggtggttgtg gttatgtgca 360
ggaccttagc tcggacctgc aagttggcgt tattaagcca tggttgctcc tagggtcaca 420
agatgctgct catgatttgg atacactgaa aaagaataag gtgactcata ttcttaatgt 480
tgcatatgga gttgaaaatg ctttcctcag tgactttaca tataagagca tttctatatt 540
ggatctgcct gaaaccaaca tcctgtctta ttttccagaa tgttttgaat ttattgaaga 600
agcaaaaaga aaagatggag tggttcttgt tcattgtaat gcaggcgttt ccagggctgc 660
tgcaattgta ataggtttcc tgatgaattc tgaacaaacc tcatttacca gtgctttttc 720
tttggtgaaa aatgcaagac cttccatatg tccaaattct ggcttcatgg agcagcttcg 780
tacatatcaa gagggcaaag aaagcaataa gtgtgacaga atacaggaga acagttcatg 840
agttgcattg tagcagacaa tggacaactg tagtttctga attgacttct atagccatct 900
tttccctttt ttggagagta gactagcaaa actccctttt ttctcttgcc ttttttatgc 960
ataaatggag gtcaatctga ttgtcctgac ctactgtata agtaaatttc aaatgtcatt 1020
actttctctt tgttattata atgtgtgatt aaatgctttt ttaaattgct aagggaaaat 1080
aaaaaaa                                                          1087
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<210> 113
<211> 217
<212> PRT
<213> Homo sapiens

<400> 113

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Met Tyr Ser Leu Asn Gln Glu Ile Lys Ala Phe Ser Arg Asn Asn Leu
 1               5                  10                  15
Arg Lys Gln Cys Thr Arg Val Thr Thr Leu Thr Gly Lys Lys Ile Ile
            20                  25                  30
Glu Thr Trp Lys Asp Ala Arg Ile His Val Val Glu Glu Val Glu Pro
        35                  40                  45
Ser Ser Gly Gly Gly Cys Gly Tyr Val Gln Asp Leu Ser Ser Asp Leu
    50                  55                  60
Gln Val Gly Val Ile Lys Pro Trp Leu Leu Leu Gly Ser Gln Asp Ala
65                  70                  75                  80
Ala His Asp Leu Asp Thr Leu Lys Lys Asn Lys Val Thr His Ile Leu
                85                  90                  95
```

```
Asn Val Ala Tyr Gly Val Glu Asn Ala Phe Leu Ser Asp Phe Thr Tyr
            100                 105                 110
Lys Ser Ile Ser Ile Leu Asp Leu Pro Glu Thr Asn Ile Leu Ser Tyr
        115                 120                 125
Phe Pro Glu Cys Phe Glu Phe Ile Glu Glu Ala Lys Arg Lys Asp Gly
    130                 135                 140
Val Val Leu Val His Cys Asn Ala Gly Val Ser Arg Ala Ala Ala Ile
145                 150                 155                 160
Val Ile Gly Phe Leu Met Asn Ser Glu Gln Thr Ser Phe Thr Ser Ala
                165                 170                 175
Phe Ser Leu Val Lys Asn Ala Arg Pro Ser Ile Cys Pro Asn Ser Gly
            180                 185                 190
Phe Met Glu Gln Leu Arg Thr Tyr Gln Glu Gly Lys Glu Ser Asn Lys
        195                 200                 205
Cys Asp Arg Ile Gln Glu Asn Ser Ser
    210                 215
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<210> 114
<211> 1106
<212> DNA
<213> Homo sapiens

<400> 114

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gacgcgtggc catgttggag gctccgggcc cgagtgatgg ctgcgagctc agcaacccca 60
gcgccagcag agtcagctgt gccgggcaga tgctggaagt gcagccagga ttgtatttcg 120
gtggggccgc ggccgtcgcg gagccagatc acctgaggga agcgggcatc acggccgtgc 180
taacagtgga ctcggaggag cccagcttca aggcggggcc tggggtcgag gatctatggc 240
gcctcttcgt gccagcgctg gacaaacccg agacggacct actcagccat ctggaccggt 300
gcgtggcctt catcggtcag gcccgcgctg agggccgtgc ggtgttggtg cactgtcatg 360
caggagtcag tcgaagtgtg gccataataa ctgcttttct catgaagact gaccaacttc 420
cctttgaaaa agcctatgaa aagctccaga ttctcaaacc agaggctaag atgaatgagg 480
ggtttgagtg gcaactgaaa ttataccagg caatgggata cgaagtggat acctctagtg 540
caatttataa gcaatatcgt ttacaaaagg ttacagagaa gtatccagaa ttgcagaatt 600
tacctcaaga actctttgct gttgacccaa ctaccgtttc acaaggattg aaagatgagg 660
ttctctacaa gtgtagaaag tgcaggcgat cattatttcg aagttctagt attctggatc 720
accgtgaagg aagtggacct atagcctttg cccacaagag aatgacacca tcttccatgc 780
ttaccacagg gaggcaagct caatgtacat cttatttcat tgaacctgta cagtggatgg 840
aatctgcttt gttgggagtg atggatggac agcttctttg cccaaaatgc agtgccaagt 900
tgggttcctt caactggtat ggtgaacagt gctcttgtgg taggtggata acacctgctt 960
ttcaaataca taagaataga gtggatgaaa tgaaaatatt gcctgttttg ggatcacaaa 1020
caggaaaaat atgaacatga tattttatag cttgggaaga aacttgcaga tgatatgtgc 1080
tgcctttgct tcttatcatt catggc                                      1106
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<210> 115
<211> 340
<212> PRT
<213> Homo sapiens

<400> 115

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Met Leu Glu Ala Pro Gly Pro Ser Asp Gly Cys Glu Leu Ser Asn Pro
 1               5                  10                  15
Ser Ala Ser Arg Val Ser Cys Ala Gly Gln Met Leu Glu Val Gln Pro
            20                  25                  30
Gly Leu Tyr Phe Gly Gly Ala Ala Ala Val Ala Glu Pro Asp His Leu
        35                  40                  45
Arg Glu Ala Gly Ile Thr Ala Val Leu Thr Val Asp Ser Glu Glu Pro
    50                  55                  60
```

```
Ser Phe Lys Ala Gly Pro Gly Val Glu Asp Leu Trp Arg Leu Phe Val
65                  70                  75                  80
Pro Ala Leu Asp Lys Pro Glu Thr Asp Leu Leu Ser His Leu Asp Arg
                85                  90                  95
Cys Val Ala Phe Ile Gly Gln Ala Arg Ala Glu Gly Arg Ala Val Leu
            100                 105                 110
Val His Cys His Ala Gly Val Ser Arg Ser Val Ala Ile Ile Thr Ala
        115                 120                 125
Phe Leu Met Lys Thr Asp Gln Leu Pro Phe Glu Lys Ala Tyr Glu Lys
    130                 135                 140
Leu Gln Ile Leu Lys Pro Glu Ala Lys Met Asn Glu Gly Phe Glu Trp
145                 150                 155                 160
Gln Leu Lys Leu Tyr Gln Ala Met Gly Tyr Glu Val Asp Thr Ser Ser
                165                 170                 175
Ala Ile Tyr Lys Gln Tyr Arg Leu Gln Lys Val Thr Glu Lys Tyr Pro
            180                 185                 190
Glu Leu Gln Asn Leu Pro Gln Glu Leu Phe Ala Val Asp Pro Thr Thr
        195                 200                 205
Val Ser Gln Gly Leu Lys Asp Glu Val Leu Tyr Lys Cys Arg Lys Cys
    210                 215                 220
Arg Arg Ser Leu Phe Arg Ser Ser Ser Ile Leu Asp His Arg Glu Gly
225                 230                 235                 240
Ser Gly Pro Ile Ala Phe Ala His Lys Arg Met Thr Pro Ser Ser Met
                245                 250                 255
Leu Thr Thr Gly Arg Gln Ala Gln Cys Thr Ser Tyr Phe Ile Glu Pro
            260                 265                 270
Val Gln Trp Met Glu Ser Ala Leu Leu Gly Val Met Asp Gly Gln Leu
        275                 280                 285
Leu Cys Pro Lys Cys Ser Ala Lys Leu Gly Ser Phe Asn Trp Tyr Gly
    290                 295                 300
Glu Gln Cys Ser Cys Gly Arg Trp Ile Thr Pro Ala Phe Gln Ile His
305                 310                 315                 320
Lys Asn Arg Val Asp Glu Met Lys Ile Leu Pro Val Leu Gly Ser Gln
                325                 330                 335
Thr Gly Lys Ile
            340
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<210> 116
<211> 1017
<212> DNA
<213> Homo sapiens

<400> 116

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gcgccagcag agtcagctgt gccgggcaga tgctggaagt gcagccagga ttgtatttcg 120
gtggggccgc ggccgtcgcg gagccagatc acctgaggga agcgggcatc acggccgtgc 180
taacagtgga ctcggaggag cccagcttca aggcggggcc tggggtcgag gatctatggc 240
gcctcttcgt gccagcgctg gacaaacccg agacggacct actcagccat ctggaccggt 300
gcgtggcctt catcggtcag gcccgcgctg agggccgtgc ggtgttggtg cactgtcatg 360
caggagtcag tcgaagtgtg gccataataa ctgcttttct catgaagact gaccaacttc 420
cctttgaaaa agcctatgaa aagctccaga ttctcaaacc agaggctaag atgaatgagg 480
ggtttgagtg gcaactgaaa ttataccagg caatgggata cgaagtggat acctctagtg 540
caatttataa gcaatatcgt ttacaaaagg ttacagagaa gtatccagaa ttgcagaatt 600
tacctcaaga actctttgct gttgacccaa ctaccgtttc acaaggattg aaagatgagg 660
ttctctacaa gtgtagaaag tgcaggcgat cattatttcg aagttctagt attctggatc 720
accgtgaagg aagtggacct atagcctttg cccacaagag aatgacacca tcttccatgc 780
ttaccacagg gaggcaagct caatgtacat cttatttcat tgaacctgta cagtggatgg 840
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aatctgcttt gttgggagtg atggatggac aggtgagaac acattttatt ttctacaatt 900
ttattttatg atctatattt tattccttct tgcattttaa gctctatttt aactagtgtt 960
ttgctccatt tcttaatttc tttatttctg atgattatat ctttcttgtg tagataa 1017

<210> 117
<211> 299
<212> PRT
<213> Homo sapiens

<400> 117
Met Leu Glu Ala Pro Gly Pro Ser Asp Gly Cys Glu Leu Ser Asn Pro
1 5 10 15
Ser Ala Ser Arg Val Ser Cys Ala Gly Gln Met Leu Glu Val Gln Pro
20 25 30
Gly Leu Tyr Phe Gly Gly Ala Ala Ala Val Ala Glu Pro Asp His Leu
35 40 45
Arg Glu Ala Gly Ile Thr Ala Val Leu Thr Val Asp Ser Glu Glu Pro
50 55 60
Ser Phe Lys Ala Gly Pro Gly Val Glu Asp Leu Trp Arg Leu Phe Val
65 70 75 80
Pro Ala Leu Asp Lys Pro Glu Thr Asp Leu Leu Ser His Leu Asp Arg
85 90 95
Cys Val Ala Phe Ile Gly Gln Ala Arg Ala Glu Gly Arg Ala Val Leu
100 105 110
Val His Cys His Ala Gly Val Ser Arg Ser Val Ala Ile Ile Thr Ala
115 120 125
Phe Leu Met Lys Thr Asp Gln Leu Pro Phe Glu Lys Ala Tyr Glu Lys
130 135 140
Leu Gln Ile Leu Lys Pro Glu Ala Lys Met Asn Glu Gly Phe Glu Trp
145 150 155 160
Gln Leu Lys Leu Tyr Gln Ala Met Gly Tyr Glu Val Asp Thr Ser Ser
165 170 175
Ala Ile Tyr Lys Gln Tyr Arg Leu Gln Lys Val Thr Glu Lys Tyr Pro
180 185 190
Glu Leu Gln Asn Leu Pro Gln Glu Leu Phe Ala Val Asp Pro Thr Thr
195 200 205
Val Ser Gln Gly Leu Lys Asp Glu Val Leu Tyr Lys Cys Arg Lys Cys
210 215 220
Arg Arg Ser Leu Phe Arg Ser Ser Ser Ile Leu Asp His Arg Glu Gly
225 230 235 240
Ser Gly Pro Ile Ala Phe Ala His Lys Arg Met Thr Pro Ser Ser Met
245 250 255
Leu Thr Thr Gly Arg Gln Ala Gln Cys Thr Ser Tyr Phe Ile Glu Pro
260 265 270
Val Gln Trp Met Glu Ser Ala Leu Leu Gly Val Met Asp Gly Gln Val
275 280 285
Arg Thr His Phe Ile Phe Tyr Asn Phe Ile Leu
290 295

<210> 118
<211> 1300
<212> DNA
<213> Homo sapiens

<400> 118
cgggctggcc catggctgag acctctctcc cagagctggg gggagaggac aaagccacgc 60
cttgccccag catcctggag ctggaggagc tcctgcgggc agggaagtct tcttgcagcc 120

gtgtggacga agtttggccc aacctttttca taggagatgc agctggtcct tactccctgc 180
catggggctc tgccactttg ccaccctggc actgatcctg ctggtgctgc tggaggctct 240
ggcccaggcg gacacacaga agatggtgga agcccagcgt ggggtcggcc ctagagcctg 300
ctactccatc tggctcctcc tggcgcctac acccctctc agccactgtc ttcagtctcc 360
acagaaacag catcaagtgt gcggagacag gcggctgaaa gccagcagca cgaactgccc 420
gtcagagaag tgcacagcct gggccagata ctcccacagg atggactcac tgcagaagca 480
ggacctccgg aggcccgaga tccatggggc agtccaggca tctccctacc agccgcccac 540
attggcttcg ctgcagcgct tgctgtgggt ccgtcaggct gccacactga accatatcga 600
tgaggtctgg cccagcctct tcctgggaga tgcgtacgca gcccgggaca agagcaagct 660
gatccagctg ggaatcaccc acgttgtgaa tgccgctgca ggcaagttcc aggtggacac 720
aggtgccaaa ttctaccgtg gaatgtccct ggagtactat ggcatcgagg cggacgacaa 780
ccccttcttc gacctcagtg tctactttct gcctgttgct cgatacatcc gagctgccct 840
cagtgttccc caaggccgcg tgctggtaca ctgtgccatg ggggtaagcc gctctgccac 900
acttgtcctg gccttcctca tgatctgtga gaacatgacg ctggtagagg ccatccagac 960
ggtgcaggcc caccgcaata tctgccctaa ctcaggcttc ctccggcagc tccaggttct 1020
ggacaaccga ctggggcggg agacggggcg gttctgatct ggcaggcagc caggatccct 1080
gacccttggc ccaaccccac cagcctggcc ctgggaacag caggctctgc tgtttctagt 1140
gaccctgaga tgtaaacagc aagtgggggc tgaggcagag gcagggatag ctgggtggtg 1200
acctcttagc gggtggattt ccctgaccca attcagagat tctttatgca aaagtgagtt 1260
cagtccatct ctataataaa atattcatcg tcataaagaa 1300

<210> 119
<211> 291
<212> PRT
<213> Homo sapiens

<400> 119
Met Gly Leu Cys His Phe Ala Thr Leu Ala Leu Ile Leu Leu Val Leu
1 5 10 15
Leu Glu Ala Leu Ala Gln Ala Asp Thr Gln Lys Met Val Glu Ala Gln
20 25 30
Arg Gly Val Gly Pro Arg Ala Cys Tyr Ser Ile Trp Leu Leu Leu Ala
35 40 45
Pro Thr Pro Pro Leu Ser His Cys Leu Gln Ser Pro Gln Lys Gln His
50 55 60
Gln Val Cys Gly Asp Arg Arg Leu Lys Ala Ser Ser Thr Asn Cys Pro
65 70 75 80
Ser Glu Lys Cys Thr Ala Trp Ala Arg Tyr Ser His Arg Met Asp Ser
85 90 95
Leu Gln Lys Gln Asp Leu Arg Arg Pro Glu Ile His Gly Ala Val Gln
100 105 110
Ala Ser Pro Tyr Gln Pro Pro Thr Leu Ala Ser Leu Gln Arg Leu Leu
115 120 125
Trp Val Arg Gln Ala Ala Thr Leu Asn His Ile Asp Glu Val Trp Pro
130 135 140
Ser Leu Phe Leu Gly Asp Ala Tyr Ala Ala Arg Asp Lys Ser Lys Leu
145 150 155 160
Ile Gln Leu Gly Ile Thr His Val Val Asn Ala Ala Ala Gly Lys Phe
165 170 175
Gln Val Asp Thr Gly Ala Lys Phe Tyr Arg Gly Met Ser Leu Glu Tyr
180 185 190
Tyr Gly Ile Glu Ala Asp Asp Asn Pro Phe Phe Asp Leu Ser Val Tyr
195 200 205
Phe Leu Pro Val Ala Arg Tyr Ile Arg Ala Ala Leu Ser Val Pro Gln
210 215 220
Gly Arg Val Leu Val His Cys Ala Met Gly Val Ser Arg Ser Ala Thr
225 230 235 240
Leu Val Leu Ala Phe Leu Met Ile Cys Glu Asn Met Thr Leu Val Glu

```
                245                 250                 255
Ala Ile Gln Thr Val Gln Ala His Arg Asn Ile Cys Pro Asn Ser Gly
            260                 265                 270
Phe Leu Arg Gln Leu Gln Val Leu Asp Asn Arg Leu Gly Arg Glu Thr
        275                 280                 285
Gly Arg Phe
    290
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<210> 120
<211> 240
<212> PRT
<213> Homo sapiens

<400> 120

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Met Gly Leu Cys His Phe Ala Thr Leu Ala Leu Ile Leu Leu Val Leu
 1               5                  10                  15
Leu Glu Ala Leu Ala Gln Ala Asp Thr Gln Lys Met Val Glu Ala Gln
            20                  25                  30
Arg Gly Val Gly Pro Arg Ala Cys Tyr Ser Ile Trp Leu Leu Leu Ala
        35                  40                  45
Pro Thr Pro Pro Leu Ser His Cys Leu Gln Ser Pro Gln Lys Gln His
    50                  55                  60
Gln Val Cys Gly Asp Arg Arg Leu Lys Ala Ser Ser Thr Asn Cys Pro
65                  70                  75                  80
Ser Glu Lys Cys Thr Ala Trp Ala Arg Tyr Ser His Arg Met Asp Ser
                85                  90                  95
Leu Gln Lys Gln Asp Leu Arg Arg Pro Glu Ile His Gly Ala Val Gln
            100                 105                 110
Ala Ser Pro Tyr Gln Pro Pro Thr Leu Ala Ser Leu Gln Arg Leu Leu
        115                 120                 125
Trp Val Arg Gln Ala Ala Thr Leu Asn His Ile Asp Glu Val Trp Pro
    130                 135                 140
Ser Leu Phe Leu Gly Asp Ala Tyr Ala Ala Arg Asp Lys Ser Lys Leu
145                 150                 155                 160
Ile Gln Leu Gly Ile Thr His Val Val Asn Ala Ala Ala Gly Arg Val
                165                 170                 175
Leu Val His Cys Ala Met Gly Val Ser Arg Ser Ala Thr Leu Val Leu
            180                 185                 190
Ala Phe Leu Met Ile Cys Glu Asn Met Thr Leu Val Glu Ala Ile Gln
        195                 200                 205
Thr Val Gln Ala His Arg Asn Ile Cys Pro Asn Ser Gly Phe Leu Arg
    210                 215                 220
Gln Leu Gln Val Leu Asp Asn Arg Leu Gly Arg Glu Thr Gly Arg Phe
225                 230                 235                 240
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<210> 121
<211> 935
<212> DNA
<213> Homo sapiens

<400> 121

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attgtgacgc ccagatggga gtggtgagag gagacagaaa gagggtggtg gccgatagct 60
ggtcctcttt ctccaacacc tagcctgaga cttggcggcg cggctgctat cctgaactag 120
cttggtaagt gttgtgtccc gaaccagcgt agagagacct cggaccagcc gccttgatga 180
cagcatccgc gtcctccttt tcatcatctc agggtgtcca gcagccctcc atctacagct 240
tctcccaaat aaccagaagc ttgtttctca gcaatggtgt ggccgccaac gacaaactcc 300
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ttctgtccag caatcgcatc accgccattg tcaatgcctc ggtggaagtg gtcaacgtat 360
tcttcgaggg cattcagtac ataaaggtgc ctgttaccga tgctcgtgac tcgcgtctct 420
acgacttttt tgaccccatt gctgatctta tccacaccat cgatatgagg cagggccgta 480
cgctgctgca ctgcatggct ggagtgagcc gttccgcctc actgtgcctt gcgtacctca 540
tgaaatacca ctccatgtcg ctgctggacg cccatacatg gaccaagtcg cgccgcccca 600
tcatccggcc caacaacggc ttttgggaac agctcatcaa ttacgaattc aagctgttta 660
ataacaacac cgtgcgcatg atcaactcgc cggtaggtaa catcccctgac atctatgaga 720
aggacctacg tatgatgata tcaatgtaag ccatcccggc cagcccctga catctgccat 780
cgatcttgca ccaagactga acttgaacac tgacattttg ttagtaaaga aaaccggatg 840
gtgccttgtt aaagggcaag aaaaaaggga gggggttgga gttttgaacg tagtaagcct 900
taccttaata gaattaaaaa aaaaaaaaaa aaaaa 935

<210> 122
<211> 190
<212> PRT
<213> Homo sapiens

<400> 122
Met Thr Ala Ser Ala Ser Ser Phe Ser Ser Ser Gln Gly Val Gln Gln
1 5 10 15
Pro Ser Ile Tyr Ser Phe Ser Gln Ile Thr Arg Ser Leu Phe Leu Ser
20 25 30
Asn Gly Val Ala Ala Asn Asp Lys Leu Leu Leu Ser Ser Asn Arg Ile
35 40 45
Thr Ala Ile Val Asn Ala Ser Val Glu Val Val Asn Val Phe Phe Glu
50 55 60
Gly Ile Gln Tyr Ile Lys Val Pro Val Thr Asp Ala Arg Asp Ser Arg
65 70 75 80
Leu Tyr Asp Phe Phe Asp Pro Ile Ala Asp Leu Ile His Thr Ile Asp
85 90 95
Met Arg Gln Gly Arg Thr Leu Leu His Cys Met Ala Gly Val Ser Arg
100 105 110
Ser Ala Ser Leu Cys Leu Ala Tyr Leu Met Lys Tyr His Ser Met Ser
115 120 125
Leu Leu Asp Ala His Thr Trp Thr Lys Ser Arg Arg Pro Ile Ile Arg
130 135 140
Pro Asn Asn Gly Phe Trp Glu Gln Leu Ile Asn Tyr Glu Phe Lys Leu
145 150 155 160
Phe Asn Asn Asn Thr Val Arg Met Ile Asn Ser Pro Val Gly Asn Ile
165 170 175
Pro Asp Ile Tyr Glu Lys Asp Leu Arg Met Met Ile Ser Met
180 185 190

<210> 123
<211> 1491
<212> DNA
<213> Homo sapiens

<400> 123
cgacagcagc aggagcgtca tggccgtggc gctgtctgcg ccggcgatcc gcctttcgga 60
ctgaggccca gcgcagcgct tgcaaagagc agctacctgg caactgaacc catcatcacc 120
acagccactc ctgcagctgc cacggtttct gccacctcta agatgtgccc tggtaactgg 180
ctttgggctt ctatgacttt tatggcccgc ttctcccgga gtagctcaag gtctcctgtt 240
cgaactcgag ggaccctgga ggagatgcca accgttcaac atcctttcct caatgtcttc 300
gagttggagc ggctcctcta cacaggcaag acagcctgta accatgccga cgaggtctgg 360
ccaggcctct atctcggaga ccaggacatg gctaacaacc gccgggagct tcgccgcctg 420
ggcatcacgc acgtcctcaa tgcctcacac agccggtggc gaggcacgcc cgaggcctat 480

gaggggctgg gcatccgcta cctgggtgtt gaggcccacg actcgccagc ctttgacatg 540
agcatccact tccagacggc tgccgacttc atccaccggg cgctgagcca gccaggaggg 600
aagatcctgg tgcattgtgc tgtgggcgtg agccgatccg ccaccctggt actggcatac 660
ctcatgctgt accaccacct taccctcgtg gaggccatca agaaagtcaa agaccaccga 720
ggcatcatcc ccaaccgggg cttcctgagg cagctcctgg ccctggaccg caggctgcgg 780
cagggtctgg aagcatgagg ggaggggggag agaggtcagg ccaggcccgt gggtaggtcc 840
ctggctccca gctggagata ggaggcccag gtggcaggta gcaggaggcc cagatcaccc 900
atcctccct ggggtcagga gaggccgagc cccaggccac tgtcactctt tgtgggaggg 960
gacggggagt gaggttgggc agtgtggtgg atgggcaccc aggaagggtt gaccagggaa 1020
ggaggcagct aggctgtaga tggaagatgg tcctgggatt cgaacaccgc tgggatctgg 1080
ccagggtgct ccctgggatt cacagtccct tcccctcttt gtgcccaagt gtttccctct 1140
ctccctcacc aaaacaaaag ggccatctct gccctgcact tgtgcagaaa gtcagggata 1200
cggcaagcat gaatgcaatg gtgtagagtt gtgtgaaacc cctagcatag agacagacag 1260
cgaagagatg gtgtgaaaag cttgcagaac cagacagaga accccacaga ctttccactc 1320
caagcacagg aggaggtagc tagcgtgtga gggttggcac taggcccacg gctgctgctt 1380
gggccaaaaa catacagagg tgcatggctg gcagtcttga aattgtcact cgcttactgg 1440
atccaagcgt ctcgaggata aataaagatc atgaaaaaca aaaaaaaaaa a 1491

<210> 124
<211> 211
<212> PRT
<213> Homo sapiens

<400> 124
Met Cys Pro Gly Asn Trp Leu Trp Ala Ser Met Thr Phe Met Ala Arg
1 5 10 15
Phe Ser Arg Ser Ser Ser Arg Ser Pro Val Arg Thr Arg Gly Thr Leu
20 25 30
Glu Glu Met Pro Thr Val Gln His Pro Phe Leu Asn Val Phe Glu Leu
35 40 45
Glu Arg Leu Leu Tyr Thr Gly Lys Thr Ala Cys Asn His Ala Asp Glu
50 55 60
Val Trp Pro Gly Leu Tyr Leu Gly Asp Gln Asp Met Ala Asn Asn Arg
65 70 75 80
Arg Glu Leu Arg Arg Leu Gly Ile Thr His Val Leu Asn Ala Ser His
85 90 95
Ser Arg Trp Arg Gly Thr Pro Glu Ala Tyr Glu Gly Leu Gly Ile Arg
100 105 110
Tyr Leu Gly Val Glu Ala His Asp Ser Pro Ala Phe Asp Met Ser Ile
115 120 125
His Phe Gln Thr Ala Ala Asp Phe Ile His Arg Ala Leu Ser Gln Pro
130 135 140
Gly Gly Lys Ile Leu Val His Cys Ala Val Gly Val Ser Arg Ser Ala
145 150 155 160
Thr Leu Val Leu Ala Tyr Leu Met Leu Tyr His His Leu Thr Leu Val
165 170 175
Glu Ala Ile Lys Lys Val Lys Asp His Arg Gly Ile Ile Pro Asn Arg
180 185 190
Gly Phe Leu Arg Gln Leu Leu Ala Leu Asp Arg Arg Leu Arg Gln Gly
195 200 205
Leu Glu Ala
210

<210> 125
<211> 1830
<212> DNA
<213> Homo sapiens

<400> 125
gaagaggagc gccagatggt ggaggaatac acttatttat gaaactgtct tgagttcttc 60
ttgaattgcc agttttcagc ctcctcatgc ctccgtctcc tttagacgac agggtagtag 120
tggcactatc taggcccgtc cgacctcagg atctcaacct ttgtttagac tctagttacc 180
ttggctctgc caacccaggc agtaacagcc accctcctgt catcgccacc accgttgtgt 240
ccctcaaggc tgcgaatctg acgtatatgc cctcatccag cggctctgcc cgctcgctga 300
attgtggatg cagcagtgcc agctgctgca ctgtggcaac ctacgacaag gacaatcagg 360
cccaaaccca agccattgcc gctggcacca ccaccactgc catcggaacc tctaccacct 420
gccctgctaa ccagatggtc aacaataatg aaaatacagg ctctctaagt ccatcaagtg 480
gggtgggcag ccctgtgtca gggacccca agcagctagc cagcatcaaa ataatctacc 540
ccaatgactt ggcaaagaag atgaccaaat gcagcaagag tcacctgccg agtcagggcc 600
ctgtcatcat tgactgcagg cccttcatgg agtacaacaa gagtcacatc caaggagctg 660
tccacattaa ctgtgccgat aagatcagcc ggcggagact gcagcagggc aagatcactg 720
tcctagactt gatttcctgt agggaaggca aggactcttt caagaggatc ttttccaaag 780
aaattatagt ttatgatgag aataccaatg aaccaagccg agtgatgccc tcccagccac 840
ttcacatagt cctcgagtcc ctgaagagag aaggcaaaga acctctggtg ttgaaaggtg 900
gacttagtag ttttaagcag aaccatgaaa acctctgtga caactccctc cagctccaag 960
agtgccggga ggtggggggc ggcgcatccg cggcctcgag cttgctacct cagcccatcc 1020
ccaccacccc tgacatcgag aacgctgagc tcacccccat cttgcccttc ctgttccttg 1080
gcaatgagca ggatgctcag gacctggaca ccatgcagcg gctgaacatc ggctacgtca 1140
tcaacgtcac cactcatctt cccctctacc actatgagaa aggcctgttc aactacaagc 1200
ggctgccagc cactgacagc aacaagcaga acctgcggca gtactttgaa gaggcttttg 1260
agttcattga ggaagctcac cagtgtggga aggggcttct catccactgc caggctgggg 1320
tgtcccgctc cgccaccatc gtcatcgctt acttgatgaa gcacactcgg atgaccatga 1380
ctgatgctta taaatttgtc aaaggcaaac gaccaattat ctccccaaac cttaacttca 1440
tggggcagtt gctagagttc gaggaagacc taaacaacgg tgtgacaccg agaatcctta 1500
caccaaagct gatgggcgtg gagacggttg tgtgacaatg gtctggatgg aaaggattgc 1560
tgctctccat taggagacaa tgaggaagga ggatggattc tggttttttt tctttctttt 1620
ttttttgta gttgggagta agtttgtgaa tggaaacaaa cttgtttaaa cactttattt 1680
ttaacaagtg taagaagact ataacttttg atgccattga gattcacctc ccacaaactg 1740
acaaattaag gaggttaaag aagtaatttt tttaagccaa caataaaaat ataatgccca 1800
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1830

<210> 126
<211> 482
<212> PRT
<213> Homo sapiens

<400> 126
Met Pro Pro Ser Pro Leu Asp Asp Arg Val Val Val Ala Leu Ser Arg
1 5 10 15
Pro Val Arg Pro Gln Asp Leu Asn Leu Cys Leu Asp Ser Ser Tyr Leu
20 25 30
Gly Ser Ala Asn Pro Gly Ser Asn Ser His Pro Pro Val Ile Ala Thr
35 40 45
Thr Val Val Ser Leu Lys Ala Ala Asn Leu Thr Tyr Met Pro Ser Ser
50 55 60
Ser Gly Ser Ala Arg Ser Leu Asn Cys Gly Cys Ser Ser Ala Ser Cys
65 70 75 80
Cys Thr Val Ala Thr Tyr Asp Lys Asp Asn Gln Ala Gln Thr Gln Ala
85 90 95
Ile Ala Ala Gly Thr Thr Thr Thr Ala Ile Gly Thr Ser Thr Thr Cys
100 105 110
Pro Ala Asn Gln Met Val Asn Asn Asn Glu Asn Thr Gly Ser Leu Ser
115 120 125
Pro Ser Ser Gly Val Gly Ser Pro Val Ser Gly Thr Pro Lys Gln Leu
130 135 140

```
Ala Ser Ile Lys Ile Ile Tyr Pro Asn Asp Leu Ala Lys Lys Met Thr
145                 150                 155                 160
Lys Cys Ser Lys Ser His Leu Pro Ser Gln Gly Pro Val Ile Ile Asp
                165                 170                 175
Cys Arg Pro Phe Met Glu Tyr Asn Lys Ser His Ile Gln Gly Ala Val
            180                 185                 190
His Ile Asn Cys Ala Asp Lys Ile Ser Arg Arg Arg Leu Gln Gln Gly
        195                 200                 205
Lys Ile Thr Val Leu Asp Leu Ile Ser Cys Arg Glu Gly Lys Asp Ser
    210                 215                 220
Phe Lys Arg Ile Phe Ser Lys Glu Ile Ile Val Tyr Asp Glu Asn Thr
225                 230                 235                 240
Asn Glu Pro Ser Arg Val Met Pro Ser Gln Pro Leu His Ile Val Leu
                245                 250                 255
Glu Ser Leu Lys Arg Glu Gly Lys Glu Pro Leu Val Leu Lys Gly Gly
            260                 265                 270
Leu Ser Ser Phe Lys Gln Asn His Glu Asn Leu Cys Asp Asn Ser Leu
        275                 280                 285
Gln Leu Gln Glu Cys Arg Glu Val Gly Gly Gly Ala Ser Ala Ala Ser
    290                 295                 300
Ser Leu Leu Pro Gln Pro Ile Pro Thr Thr Pro Asp Ile Glu Asn Ala
305                 310                 315                 320
Glu Leu Thr Pro Ile Leu Pro Phe Leu Phe Leu Gly Asn Glu Gln Asp
                325                 330                 335
Ala Gln Asp Leu Asp Thr Met Gln Arg Leu Asn Ile Gly Tyr Val Ile
            340                 345                 350
Asn Val Thr Thr His Leu Pro Leu Tyr His Tyr Glu Lys Gly Leu Phe
        355                 360                 365
Asn Tyr Lys Arg Leu Pro Ala Thr Asp Ser Asn Lys Gln Asn Leu Arg
    370                 375                 380
Gln Tyr Phe Glu Glu Ala Phe Glu Phe Ile Glu Glu Ala His Gln Cys
385                 390                 395                 400
Gly Lys Gly Leu Leu Ile His Cys Gln Ala Gly Val Ser Arg Ser Ala
                405                 410                 415
Thr Ile Val Ile Ala Tyr Leu Met Lys His Thr Arg Met Thr Met Thr
            420                 425                 430
Asp Ala Tyr Lys Phe Val Lys Gly Lys Arg Pro Ile Ile Ser Pro Asn
        435                 440                 445
Leu Asn Phe Met Gly Gln Leu Leu Glu Phe Glu Glu Asp Leu Asn Asn
    450                 455                 460
Gly Val Thr Pro Arg Ile Leu Thr Pro Lys Leu Met Gly Val Glu Thr
465                 470                 475                 480
Val Val
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<210> 127
<211> 707
<212> DNA
<213> Homo sapiens

<400> 127
tgacccgctg tcctgtgccc tttcccagcg atgggcgtgc agccccccaa cttctcctgg 60
gtgcttccgg gccggctggc gggactggcg ctgccgcggc tccccgccca ctaccagttc 120
ctgttggacc tgggcgtgcg gcacctggtg tccctgacgg agcgcgggcc ccctcacagc 180
gacagctgcc ccggcctcac cctgcaccgc ctgcgcatcc ccgacttctg cccgccggcc 240
cccgaccaga tcgaccgctt cgtgcagatc gtggacgagg ccaacgcacg gggagaggct 300
gtgggagtgc actgtgctct gggctttggc cgcactggca ccatgctggc ctgttacctg 360

gtgaaggagc ggggcttggc tgcaggagat gccattgctg aaatccgacg actacgaccc 420
ggctccatcg agacctatga gcaggagaaa gcagtcttcc agttctacca gcgaacgaaa 480
taaggggcct tagtaccctt ctaccaggcc ctcactcccc ttccccatgt tgtcgatggg 540
gccagagatg aagggaagtg gactaaagta ttaaaccctc tagctcccat tggctgaaga 600
cactgaagta gcccacccct gcaggcaggt cctgattgaa ggggaggctt gtactgcttt 660
gttgaataaa tgagttttac gaaccaaaaa aaaaaaaaaa aaaaaaa 707

<210> 128
<211> 150
<212> PRT
<213> Homo sapiens

<400> 128
Met Gly Val Gln Pro Pro Asn Phe Ser Trp Val Leu Pro Gly Arg Leu
1 5 10 15
Ala Gly Leu Ala Leu Pro Arg Leu Pro Ala His Tyr Gln Phe Leu Leu
20 25 30
Asp Leu Gly Val Arg His Leu Val Ser Leu Thr Glu Arg Gly Pro Pro
35 40 45
His Ser Asp Ser Cys Pro Gly Leu Thr Leu His Arg Leu Arg Ile Pro
50 55 60
Asp Phe Cys Pro Pro Ala Pro Asp Gln Ile Asp Arg Phe Val Gln Ile
65 70 75 80
Val Asp Glu Ala Asn Ala Arg Gly Glu Ala Val Gly Val His Cys Ala
85 90 95
Leu Gly Phe Gly Arg Thr Gly Thr Met Leu Ala Cys Tyr Leu Val Lys
100 105 110
Glu Arg Gly Leu Ala Ala Gly Asp Ala Ile Ala Glu Ile Arg Arg Leu
115 120 125
Arg Pro Gly Ser Ile Glu Thr Tyr Glu Gln Glu Lys Ala Val Phe Gln
130 135 140
Phe Tyr Gln Arg Thr Lys
145 150

<210> 129
<211> 1949
<212> DNA
<213> Homo sapiens

<400> 129
aagcagtggt aacaacgcag agtacgcggg cgaggagaat atcttgctgg gagtggactt 60
ttccagtaag gaaagtaaaa gctgcaccat tgggatggtt ctccgactgt ggagcgacac 120
gaaaatccac cttgatggag atggtgggtt cagcgtgagc acagcaggaa ggatgcacat 180
atttaagcct gtgtctgtcc aggccatgtg gtctgccctg caggtgcttc acaaggcctg 240
cgaagtggcc cggaggcaca actacttccc cgggggtgta gctctcatct gggctaccta 300
ctatgagagc tgcatcagct ccgagcagag ctgcatcaac gagtggaacg ccatgcagga 360
cctggagtct acgcggcccg actcccccgc gctatttgtg gacaagccca ctgaagggga 420
aaggaccgag cgcctcatca aagccaagct ccgaagcatc atgatgagcc aggatctaga 480
aaatgtgact tccaaagaga ttcgtaatga attagagaaa cagatgaatt gtaacttgaa 540
ggaactcaag gaatttatag acaatgagat gctacttatc ttgggacaga tggacaagcc 600
ctcccttatc ttcgatcatc tttatctcgg ctctgaatgg aatgcatcca atctggagga 660
actgcagggc tcaggggttg attacatttt aaatgttacc agagaaatcg ataatttttt 720
tcctggctta tttgcatatc ataacatccg agtctacgat gaagagacca cagacctcct 780
cgcccactgg aatgaagcgt atcatttat aaacaaagcg aagaggaacc attccaagtg 840
cctggtgcat tgcaaaatgg gcgtgagtcg ctcggcctcc acagtcatag cctatgcaat 900
gaaggaattc ggctggcctc tggaaaaagc atataactat gtaaagcaga agcgcagcat 960
cacgcgcccc aacgcgggct ttatgaggca gctgtctgag tatgaaggca tcttggatgc 1020

aagcaaacag cggcacaaca agctgtggcg tcagcagaca gacagcagcc tccagcagcc 1080
tgtggatgac cctgcaggac ctggcgactt cttgccagag accccagatg gcaccccgga 1140
aagccagctg cccttcttgg atgatgccgc ccagcccggc ttagggcccc ccctcccctg 1200
ctgtttccgg cgactctcag acccccttct gccttccect gaggatgaag ccggcagctt 1260
ggtccacctg gaggatccgg agagggaggc tctgttggag gaagctgctc cacctgcaga 1320
ggtgcacagg ccggccagac agccccagca aggttccgga ctctgtgaga aggatgtgaa 1380
gaagaaacta gagtttggga gtcccaaagg tcggagcggc tccttgctgc aggtggagga 1440
gacggaaagg gaggagggcc tgggagcagg gaggtggggg cagcttccaa cccagctcga 1500
tcaaaacctg ctcaactcgg agaacctaaa caacaacagc aagaggagct gtcccaacgg 1560
catggaggta ggcagagccc ggcctgcagg gtggcacacc ccatcccttc catcccactc 1620
taattggcct acctcagcct ctgtagtagg gactacaggc acccgccacc acacccagct 1680
gatttttttc tattgtctcc tctgggcccc cagctcccat ctccagggac ctgagggttc 1740
tttcacaggg tgattctgct ggtgggtacg tagtgcatac cttatatagc aaattgagaa 1800
tctgttggga ataacacata tctctgcaca ccatcttcac cccatgtacc ttattcatac 1860
cctgggcagg gcttccaact caatttcttt ttgtgtatgt aaaattaaaa catataattt 1920
atcagccaaa aaaaaaaaaa aaaaaaaaa 1949

<210> 130
<211> 552
<212> PRT
<213> Homo sapiens

<400> 130
Met Val Leu Arg Leu Trp Ser Asp Thr Lys Ile His Leu Asp Gly Asp
1 5 10 15
Gly Gly Phe Ser Val Ser Thr Ala Gly Arg Met His Ile Phe Lys Pro
20 25 30
Val Ser Val Gln Ala Met Trp Ser Ala Leu Gln Val Leu His Lys Ala
35 40 45
Cys Glu Val Ala Arg Arg His Asn Tyr Phe Pro Gly Gly Val Ala Leu
50 55 60
Ile Trp Ala Thr Tyr Tyr Glu Ser Cys Ile Ser Ser Glu Gln Ser Cys
65 70 75 80
Ile Asn Glu Trp Asn Ala Met Gln Asp Leu Glu Ser Thr Arg Pro Asp
85 90 95
Ser Pro Ala Leu Phe Val Asp Lys Pro Thr Glu Gly Glu Arg Thr Glu
100 105 110
Arg Leu Ile Lys Ala Lys Leu Arg Ser Ile Met Met Ser Gln Asp Leu
115 120 125
Glu Asn Val Thr Ser Lys Glu Ile Arg Asn Glu Leu Glu Lys Gln Met
130 135 140
Asn Cys Asn Leu Lys Glu Leu Lys Glu Phe Ile Asp Asn Glu Met Leu
145 150 155 160
Leu Ile Leu Gly Gln Met Asp Lys Pro Ser Leu Ile Phe Asp His Leu
165 170 175
Tyr Leu Gly Ser Glu Trp Asn Ala Ser Asn Leu Glu Glu Leu Gln Gly
180 185 190
Ser Gly Val Asp Tyr Ile Leu Asn Val Thr Arg Glu Ile Asp Asn Phe
195 200 205
Phe Pro Gly Leu Phe Ala Tyr His Asn Ile Arg Val Tyr Asp Glu Glu
210 215 220
Thr Thr Asp Leu Leu Ala His Trp Asn Glu Ala Tyr His Phe Ile Asn
225 230 235 240
Lys Ala Lys Arg Asn His Ser Lys Cys Leu Val His Cys Lys Met Gly
245 250 255
Val Ser Arg Ser Ala Ser Thr Val Ile Ala Tyr Ala Met Lys Glu Phe
260 265 270
Gly Trp Pro Leu Glu Lys Ala Tyr Asn Tyr Val Lys Gln Lys Arg Ser

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        275                 280                 285
Ile Thr Arg Pro Asn Ala Gly Phe Met Arg Gln Leu Ser Glu Tyr Glu
    290                 295                 300
Gly Ile Leu Asp Ala Ser Lys Gln Arg His Asn Lys Leu Trp Arg Gln
305                 310                 315                 320
Gln Thr Asp Ser Ser Leu Gln Gln Pro Val Asp Asp Pro Ala Gly Pro
                325                 330                 335
Gly Asp Phe Leu Pro Glu Thr Pro Asp Gly Thr Pro Glu Ser Gln Leu
            340                 345                 350
Pro Phe Leu Asp Asp Ala Ala Gln Pro Gly Leu Gly Pro Pro Leu Pro
        355                 360                 365
Cys Cys Phe Arg Arg Leu Ser Asp Pro Leu Leu Pro Ser Pro Glu Asp
    370                 375                 380
Glu Thr Gly Ser Leu Val His Leu Glu Asp Pro Glu Arg Glu Ala Leu
385                 390                 395                 400
Leu Glu Glu Ala Ala Pro Pro Ala Glu Val His Arg Pro Ala Arg Gln
                405                 410                 415
Pro Gln Gln Gly Ser Gly Leu Cys Glu Lys Asp Val Lys Lys Lys Leu
            420                 425                 430
Glu Phe Gly Ser Pro Lys Gly Arg Ser Gly Ser Leu Leu Gln Val Glu
        435                 440                 445
Glu Thr Glu Arg Glu Glu Gly Leu Gly Ala Gly Arg Trp Gly Gln Leu
    450                 455                 460
Pro Thr Gln Leu Asp Gln Asn Leu Leu Asn Ser Glu Asn Leu Asn Asn
465                 470                 475                 480
Asn Ser Lys Arg Ser Cys Pro Asn Gly Met Glu Val Gly Arg Ala Arg
                485                 490                 495
Pro Ala Gly Trp His Thr Pro Ser Leu Pro Ser His Ser Asn Trp Pro
            500                 505                 510
Thr Ser Ala Ser Val Val Gly Thr Thr Gly Thr Arg His His Thr Gln
        515                 520                 525
Leu Ile Phe Phe Tyr Cys Leu Leu Trp Ala Pro Ser Ser His Leu Gln
    530                 535                 540
Gly Pro Glu Gly Ser Phe Thr Gly
545                 550
```

<210> 131
<211> 1711
<212> DNA
<213> Homo sapiens

<400> 131

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cctgggaaga agttatctat ctctcgagtg acattcaaga tataccgtac ccctcggttc 60
tgtaagtcct ctaagttgga ggcattccat tctgagccgg ccccatgacc ctgagcacgt 120
tggcccgcaa gaggaaggcg cccctcgctt gcacctgcag cctcggtggc cccgacatga 180
ttccttactt ctccgccaac gcggtcatct cgcagaacgc catcaaccag ctcatcagcg 240
agagctttct aactgtcaaa ggtgctgccc tttttctacc acggggaaat ggctcatcca 300
caccaagaat cagccacaga cggaacaagc atgcaggcga tctccaacag catctccaag 360
caatgttcat tttactccgc ccagaagaca acatcaggct ggctgtaaga ctggaaagta 420
cttaccagaa tcgaacacgc tatatggtag tggtttcaac taatggtaga caagacactg 480
aagaaagcat cgtcctagga atggatttct cctctaatga cagtagcact tgtaccatgg 540
gcttagtttt gcctctctgg agcgacacgc taattcattt ggatggtgat ggtgggttca 600
gtgtatcgac ggataacaga gttcacatat tcaaacctgt atctgtgcag gcaatgtggt 660
ctgcactaca gagcttacac aaggcttgtg aagtcgccag agcgcataac tactacccag 720
gcagcctatt tctcacttgg gtgagttatt atgagagcca tatcaactca gatcaatcct 780
cagtcaatga atggaatgca atgcaagatg tacagtccca ccggcccgac tctccagctc 840
tcttcaccga catacctact gaacgtgaac gaacagaaag gctaattaaa accaaattaa 900
```

gggagatcat gatgcagaag gatttggaga atattacatc caaagagata agaacagagt 960
tggaaatgca aatggtgtgc aacttgcggg aattcaagga atttatagac aatgaaatga 1020
tagtgatcct tggtcaaatg gatagcccta cacagatatt tgagcatgtg ttcctgggct 1080
cagaatggaa tgcctccaac ttagaggact tacagaaccg aggggtacgg tatatcttga 1140
atgtcactcg agagatagat aacttcttcc caggagtctt tgagtatcat aacattcggg 1200
tatatgatga agaggcaacg gatctcctgg cgtactggaa tgacacttac aaattcatct 1260
ctaaagcaaa gaaacatgga tctaaatgcc ttgtgcactg caaaatgggg gtgagtcgct 1320
cagcctccac cgtgattgcc tatgcaatga aggaatatgg ctggaatctg gaccgagcct 1380
atgactatgt gaaagaaaga cgaacggtaa ccaagcccaa cccaagcttc atgagacaac 1440
tggaagagta tcaggggatc ttgctggcaa gcttcctagg cttgattcat ggagggaggg 1500
acaagccctg gggagagaaa agcacagaat ttgagtcagt agatctggtt tccattcctg 1560
gttcaccctc ttgctgcaac cctgagaagt tacttcacat ttctcatcct tacctgaccc 1620
catctataaa atgaaaatca agagatccat ctcacagggt tattgtgaat aaaaatgtgt 1680
ttgaatgttt ataaaaaaaa aaaaaaaaaa a 1711

<210> 132
<211> 509
<212> PRT
<213> Homo sapiens

<400> 132
Met Thr Leu Ser Thr Leu Ala Arg Lys Arg Lys Ala Pro Leu Ala Cys
1 5 10 15
Thr Cys Ser Leu Gly Gly Pro Asp Met Ile Pro Tyr Phe Ser Ala Asn
20 25 30
Ala Val Ile Ser Gln Asn Ala Ile Asn Gln Leu Ile Ser Glu Ser Phe
35 40 45
Leu Thr Val Lys Gly Ala Ala Leu Phe Leu Pro Arg Gly Asn Gly Ser
50 55 60
Ser Thr Pro Arg Ile Ser His Arg Arg Asn Lys His Ala Gly Asp Leu
65 70 75 80
Gln Gln His Leu Gln Ala Met Phe Ile Leu Leu Arg Pro Glu Asp Asn
85 90 95
Ile Arg Leu Ala Val Arg Leu Glu Ser Thr Tyr Gln Asn Arg Thr Arg
100 105 110
Tyr Met Val Val Val Ser Thr Asn Gly Arg Gln Asp Thr Glu Glu Ser
115 120 125
Ile Val Leu Gly Met Asp Phe Ser Ser Asn Asp Ser Ser Thr Cys Thr
130 135 140
Met Gly Leu Val Leu Pro Leu Trp Ser Asp Thr Leu Ile His Leu Asp
145 150 155 160
Gly Asp Gly Gly Phe Ser Val Ser Thr Asp Asn Arg Val His Ile Phe
165 170 175
Lys Pro Val Ser Val Gln Ala Met Trp Ser Ala Leu Gln Ser Leu His
180 185 190
Lys Ala Cys Glu Val Ala Arg Ala His Asn Tyr Tyr Pro Gly Ser Leu
195 200 205
Phe Leu Thr Trp Val Ser Tyr Tyr Glu Ser His Ile Asn Ser Asp Gln
210 215 220
Ser Ser Val Asn Glu Trp Asn Ala Met Gln Asp Val Gln Ser His Arg
225 230 235 240
Pro Asp Ser Pro Ala Leu Phe Thr Asp Ile Pro Thr Glu Arg Glu Arg
245 250 255
Thr Glu Arg Leu Ile Lys Thr Lys Leu Arg Glu Ile Met Met Gln Lys
260 265 270
Asp Leu Glu Asn Ile Thr Ser Lys Glu Ile Arg Thr Glu Leu Glu Met
275 280 285
Gln Met Val Cys Asn Leu Arg Glu Phe Lys Glu Phe Ile Asp Asn Glu

```
    290                 295                 300
Met Ile Val Ile Leu Gly Gln Met Asp Ser Pro Thr Gln Ile Phe Glu
305                 310                 315                 320
His Val Phe Leu Gly Ser Glu Trp Asn Ala Ser Asn Leu Glu Asp Leu
                325                 330                 335
Gln Asn Arg Gly Val Arg Tyr Ile Leu Asn Val Thr Arg Glu Ile Asp
            340                 345                 350
Asn Phe Phe Pro Gly Val Phe Glu Tyr His Asn Ile Arg Val Tyr Asp
        355                 360                 365
Glu Glu Ala Thr Asp Leu Leu Ala Tyr Trp Asn Asp Thr Tyr Lys Phe
    370                 375                 380
Ile Ser Lys Ala Lys Lys His Gly Ser Lys Cys Leu Val His Cys Lys
385                 390                 395                 400
Met Gly Val Ser Arg Ser Ala Ser Thr Val Ile Ala Tyr Ala Met Lys
                405                 410                 415
Glu Tyr Gly Trp Asn Leu Asp Arg Ala Tyr Asp Tyr Val Lys Glu Arg
            420                 425                 430
Arg Thr Val Thr Lys Pro Asn Pro Ser Phe Met Arg Gln Leu Glu Glu
        435                 440                 445
Tyr Gln Gly Ile Leu Leu Ala Ser Phe Leu Gly Leu Ile His Gly Gly
    450                 455                 460
Arg Asp Lys Pro Trp Gly Glu Lys Ser Thr Glu Phe Glu Ser Val Asp
465                 470                 475                 480
Leu Val Ser Ile Pro Gly Ser Pro Ser Cys Cys Asn Pro Glu Lys Leu
                485                 490                 495
Leu His Ile Ser His Pro Tyr Leu Thr Pro Ser Ile Lys
            500                 505
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<210> 133
<211> 1165
<212> DNA
<213> Homo sapiens

<400> 133

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ggccagtggg ggtggctggg cgtgcggctg ctacatgccc cacggaccag aacctcccga 60
cgcggccagg ccccggcaca cccagctgca gaaaggagag aaaatccctt ggctctaaaa 120
tgacatctgg agaagtgaag acaagcctca agaatgccta ctcatctgcc aagaggctgt 180
cgccgaagat ggaggaggaa ggggaggagg aggactactg caccctgga gcctttgagc 240
tggagcggct cttctggaag ggcagtcccc agtacaccca cgtcaacgag gtctggccca 300
agctctacat tggcgatgag gcgacggcgc tggaccgcta taggctgcag aaggcggggt 360
tcacgcacgt gctgaacgcg gcccacggcc gctggaacgt ggacactggg cccgactact 420
accgcgacat ggacatccag taccacggcg tggaggccga cgacctgccc accttcgacc 480
tcagtgtctt cttctacccg gcggcagcct tcatcgacag agcgctaagc gacgaccaca 540
gtaagatcct ggttcactgc gtcatgggcc gcagccggtc agccaccctg gtcctggcct 600
acctgatgat ccacaaggac atgaccctgg tggacgccat ccagcaagtg gccaagaacc 660
gctgcgtcct cccgaaccgg ggctttttga agcagctccg ggagctggac aagcagctgg 720
tgcagcagag gcgacggtcc cagcgccagg acggtgagga ggaggatggc agggagctgt 780
aggcccgact cacagggcca gcagaggcac ttggggacag aggggagagg cagaacatag 840
ccctggccta ggactccaga gaagggatgg tgaaaccgaa gctcgactct tccaaaccat 900
cttgttcaac ttccccatgt gtgctgggga cagggaggac ccagagctgc ccccgggcag 960
agctgagcgc tcagcctctc agcaaaatgg gagggacggg ctccccggct ctgggtcaca 1020
gaggagcatg ccacgctgca ccaagtctcc tgctttggtt ttgtttttt ggtgagaagg 1080
aagagggaaa aagattttta aaatgtgtag gcagtatgtt gtgattaaac gtttggcttt 1140
gtccaaaaaa aaaaaaaaaa aaaaa                                      1165
```

<210> 134
<211> 220

<212> PRT
<213> Homo sapiens

<400> 134
Met Thr Ser Gly Glu Val Lys Thr Ser Leu Lys Asn Ala Tyr Ser Ser
1 5 10 15
Ala Lys Arg Leu Ser Pro Lys Met Glu Glu Glu Gly Glu Glu Glu Asp
20 25 30
Tyr Cys Thr Pro Gly Ala Phe Glu Leu Glu Arg Leu Phe Trp Lys Gly
35 40 45
Ser Pro Gln Tyr Thr His Val Asn Glu Val Trp Pro Lys Leu Tyr Ile
50 55 60
Gly Asp Glu Ala Thr Ala Leu Asp Arg Tyr Arg Leu Gln Lys Ala Gly
65 70 75 80
Phe Thr His Val Leu Asn Ala Ala His Gly Arg Trp Asn Val Asp Thr
85 90 95
Gly Pro Asp Tyr Tyr Arg Asp Met Asp Ile Gln Tyr His Gly Val Glu
100 105 110
Ala Asp Asp Leu Pro Thr Phe Asp Leu Ser Val Phe Phe Tyr Pro Ala
115 120 125
Ala Ala Phe Ile Asp Arg Ala Leu Ser Asp Asp His Ser Lys Ile Leu
130 135 140
Val His Cys Val Met Gly Arg Ser Arg Ser Ala Thr Leu Val Leu Ala
145 150 155 160
Tyr Leu Met Ile His Lys Asp Met Thr Leu Val Asp Ala Ile Gln Gln
165 170 175
Val Ala Lys Asn Arg Cys Val Leu Pro Asn Arg Gly Phe Leu Lys Gln
180 185 190
Leu Arg Glu Leu Asp Lys Gln Leu Val Gln Gln Arg Arg Arg Ser Gln
195 200 205
Arg Gln Asp Gly Glu Glu Glu Asp Gly Arg Glu Leu
210 215 220

<210> 135
<211> 1980
<212> DNA
<213> Homo sapiens

<400> 135
atggccctgg tcacagtgag ccgttcgccc ccgggcagcg gcgcctccac gcccgtgggg 60
ccctgggacc aggcggtcca gcgaaggagt cgactccagc gaaggcagag ctttgcggtg 120
ctccgtgggg ctgtcctggg actgcaggat ggaggggaca atgatgatgc agcagaggcc 180
agttctgagc caacagagaa ggccccgagt gaggaggagc tccacgggga ccagacagac 240
ttcgggcaag gatcccagag tccccagaag caggaggagc agaggcagca cctgcacctc 300
atggtacagc tgctgaggcc gcaggatgac atccgcctgg cagcccagct ggaggcaccc 360
cggcctcccc ggctccgcta cctgctggta gtttctacac gagaaggaga aggtctgagc 420
caggatgaga cggtcctcct gggcgtggat ttccctgaca gcagctcccc cagctgcacc 480
ctgggcctgg tcttgccccc ctggagtgac acccaggtgt acttagatgg agacgggggc 540
ttcagcgtga cgtctggtgg gcaaagccgg atcttcaagc ccatctccat ccagaccatg 600
tgggccacac tccaggtatt gcaccaagca tgtgaggcag ctctaggcag cggccttgta 660
ccgggtggca gtgccctcac ctgggccagc cactaccagg agagactgaa ctccgaacag 720
agctgcctca atgagtggac ggctatggcc gacctggagt ctctgcggcc tcccagcgcc 780
gagcctggcg ggtcctcaga acaggagcag atggagcagg cgatccgtgc tgagctgtgg 840
aaagtgttgg atgtcagtga cctggagagt gtcacttcca aagagatccg ccaggctctg 900
gagctgcgcc tggggctccc cctccagcag taccgtgact tcatcgacaa ccagatgctg 960
ctgctggtgg cacagcggga ccgagcctcc cgcatcttcc cccacctcta cctgggctca 1020
gagtggaacg cagcaaacct ggaggagctg cagaggaaca gggtcaccca catcttgaac 1080

atggcccggg agattgacaa cttctaccct gagcgcttca cctaccacaa tgtgcgcctc 1140
tgggatgagg agtcggccca gctgctgccg cactggaagg agacgcaccg cttcattgag 1200
gctgcaagag cacagggcac ccacgtgctg gtccactgca agatgggcgt cagccgctca 1260
gcggccacag tgctggccta tgccatgaag cagtacgaat gcagcctgga gcaggccctg 1320
cgccacgtgc aggagctccg gcccatcgcc cgccccaacc ctggcttcct gcgccagctg 1380
cagatctacc agggcatcct gacggccagc cgccagagcc atgtctggga gcagaaagtg 1440
ggtggggtct ccccagagga gcacccagcc cctgaagtct ctacaccatt cccacctctt 1500
ccgccagaac ctgagggtgg tggggaggag aaggttgtag gcatggaaga gagccaggca 1560
gccccgaaag aagagcctgg gccacggcca cgtataaacc tccgaggggt catgaggtcc 1620
atcagtcttc tggagccctc cttggagctg gagagcacct cagagaccag tgacatgcca 1680
gaggtcttct cttcccacga gtcttcacat gaagagcctc tgcagccctt cccacagctt 1740
gcaaggacca agggaggcca gcaggtggac agggggcctc agcctgccct gaagtcccgc 1800
cagtcagtgg ttaccctcca gggcagtgcc gtggtggcca accggaccca ggccttccag 1860
gagcaggagc aggggcaggg gcaggggcag ggagagccct gcatttcctc tacgcccagg 1920
ttccggaagg tggtgagaca ggccagcgtg catgacagtg gagaggaggg cgaggcctga 1980

<210> 136
<211> 659
<212> PRT
<213> Homo sapiens

<400> 136
Met Ala Leu Val Thr Val Ser Arg Ser Pro Pro Gly Ser Gly Ala Ser
1 5 10 15
Thr Pro Val Gly Pro Trp Asp Gln Ala Val Gln Arg Arg Ser Arg Leu
20 25 30
Gln Arg Arg Gln Ser Phe Ala Val Leu Arg Gly Ala Val Leu Gly Leu
35 40 45
Gln Asp Gly Gly Asp Asn Asp Asp Ala Ala Glu Ala Ser Ser Glu Pro
50 55 60
Thr Glu Lys Ala Pro Ser Glu Glu Glu Leu His Gly Asp Gln Thr Asp
65 70 75 80
Phe Gly Gln Gly Ser Gln Ser Pro Gln Lys Gln Glu Glu Gln Arg Gln
85 90 95
His Leu His Leu Met Val Gln Leu Leu Arg Pro Gln Asp Asp Ile Arg
100 105 110
Leu Ala Ala Gln Leu Glu Ala Pro Arg Pro Pro Arg Leu Arg Tyr Leu
115 120 125
Leu Val Val Ser Thr Arg Glu Gly Glu Gly Leu Ser Gln Asp Glu Thr
130 135 140
Val Leu Leu Gly Val Asp Phe Pro Asp Ser Ser Ser Pro Ser Cys Thr
145 150 155 160
Leu Gly Leu Val Leu Pro Leu Trp Ser Asp Thr Gln Val Tyr Leu Asp
165 170 175
Gly Asp Gly Gly Phe Ser Val Thr Ser Gly Gly Gln Ser Arg Ile Phe
180 185 190
Lys Pro Ile Ser Ile Gln Thr Met Trp Ala Thr Leu Gln Val Leu His
195 200 205
Gln Ala Cys Glu Ala Ala Leu Gly Ser Gly Leu Val Pro Gly Gly Ser
210 215 220
Ala Leu Thr Trp Ala Ser His Tyr Gln Glu Arg Leu Asn Ser Glu Gln
225 230 235 240
Ser Cys Leu Asn Glu Trp Thr Ala Met Ala Asp Leu Glu Ser Leu Arg
245 250 255
Pro Pro Ser Ala Glu Pro Gly Gly Ser Ser Glu Gln Glu Gln Met Glu
260 265 270
Gln Ala Ile Arg Ala Glu Leu Trp Lys Val Leu Asp Val Ser Asp Leu

```
        275                 280                 285
Glu Ser Val Thr Ser Lys Glu Ile Arg Gln Ala Leu Glu Leu Arg Leu
    290                 295                 300
Gly Leu Pro Leu Gln Gln Tyr Arg Asp Phe Ile Asp Asn Gln Met Leu
305                 310                 315                 320
Leu Leu Val Ala Gln Arg Asp Arg Ala Ser Arg Ile Phe Pro His Leu
                325                 330                 335
Tyr Leu Gly Ser Glu Trp Asn Ala Ala Asn Leu Glu Glu Leu Gln Arg
            340                 345                 350
Asn Arg Val Thr His Ile Leu Asn Met Ala Arg Glu Ile Asp Asn Phe
        355                 360                 365
Tyr Pro Glu Arg Phe Thr Tyr His Asn Val Arg Leu Trp Asp Glu Glu
    370                 375                 380
Ser Ala Gln Leu Leu Pro His Trp Lys Glu Thr His Arg Phe Ile Glu
385                 390                 395                 400
Ala Ala Arg Ala Gln Gly Thr His Val Leu Val His Cys Lys Met Gly
                405                 410                 415
Val Ser Arg Ser Ala Ala Thr Val Leu Ala Tyr Ala Met Lys Gln Tyr
            420                 425                 430
Glu Cys Ser Leu Glu Gln Ala Leu Arg His Val Gln Glu Leu Arg Pro
        435                 440                 445
Ile Ala Arg Pro Asn Pro Gly Phe Leu Arg Gln Leu Gln Ile Tyr Gln
    450                 455                 460
Gly Ile Leu Thr Ala Ser Arg Gln Ser His Val Trp Glu Gln Lys Val
465                 470                 475                 480
Gly Gly Val Ser Pro Glu Glu His Pro Ala Pro Glu Val Ser Thr Pro
                485                 490                 495
Phe Pro Pro Leu Pro Pro Glu Pro Glu Gly Gly Gly Glu Glu Lys Val
            500                 505                 510
Val Gly Met Glu Glu Ser Gln Ala Ala Pro Lys Glu Glu Pro Gly Pro
        515                 520                 525
Arg Pro Arg Ile Asn Leu Arg Gly Val Met Arg Ser Ile Ser Leu Leu
    530                 535                 540
Glu Pro Ser Leu Glu Leu Glu Ser Thr Ser Glu Thr Ser Asp Met Pro
545                 550                 555                 560
Glu Val Phe Ser Ser His Glu Ser Ser His Glu Glu Pro Leu Gln Pro
                565                 570                 575
Phe Pro Gln Leu Ala Arg Thr Lys Gly Gly Gln Gln Val Asp Arg Gly
            580                 585                 590
Pro Gln Pro Ala Leu Lys Ser Arg Gln Ser Val Val Thr Leu Gln Gly
        595                 600                 605
Ser Ala Val Val Ala Asn Arg Thr Gln Ala Phe Gln Glu Gln Glu Gln
    610                 615                 620
Gly Gln Gly Gln Gly Gln Gly Glu Pro Cys Ile Ser Ser Thr Pro Arg
625                 630                 635                 640
Phe Arg Lys Val Val Arg Gln Ala Ser Val His Asp Ser Gly Glu Glu
                645                 650                 655
Gly Glu Ala
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<210> 137
<211> 1416
<212> DNA
<213> Mus musculus

<400> 137
atggccctgg tcacagtgag ccgttcgccc ccgggcagcg gcgcctccac gcccgtgggg 60

ccctgggacc aggcggtcca gcgaaggagt cgactccagc gaaggcagag ctttgcggtg 120
ctccgtgggg ctgtcctggg actgcaggat ggaggggaca atgatgatgc agcagaggcc 180
agttctgagc caacagagaa ggccccgagt gaggaggagc tccacgggga ccagacagac 240
ttcgggcaag gatcccagag tccccagaag caggaggagc agaggcagca cctgcacctc 300
atggtacagc tgctgaggcc gcaggatgac atccgcctgg cagcccagct ggaggcaccc 360
cggcctcccc ggctccgcta cctgctggta gtttctacac gagaaggaga aggtctgagc 420
caggatgaga cggtcctcct gggcgtggat ttccctgaca gcagctcccc cagctgcacc 480
ctgggcctgg tcttgccccc ctggagtgac acccaggtgt acttagatgg agacgggggc 540
ttcagcgtga cgtctggtgg gcaaagccgg atcttcaagc ccatctccat ccagaccatg 600
tgggccacac tccaggtatt gcaccaagca tgtgaggcag ctctaggcag cggccttgta 660
ccgggtggca gtgccctcac ctgggccagc cactaccagg agagactgaa ctccgaacag 720
agctgcctca atgagtggac ggctatggcc gacctggagt ctctgcggcc tcccagcgcc 780
gagcctggcg ggtcctcaga acaggagcag atggagcagg cgatccgtgc tgagctgtgg 840
aaagtgttgg atgtcagtga cctggagagt gtcacttcca aagagatccg ccaggctctg 900
gagctgcgcc tggggctccc cctccagcag taccgtgact tcatcgacaa ccagatgctg 960
ctgctggtgg cacagcggga ccgagcctcc cgcatcttcc cccacctcta cctgggctca 1020
gagtggaacg cagcaaacct ggaggagctg cagaggaaca gggtcaccca catcttgaac 1080
atggcccggg agattgacaa cttctaccct gagcgcttca cctaccacaa tgtgcgcctc 1140
tgggatgagg agtcggccca gctgctgccg cactggaagg agacgcaccg cttcattgag 1200
gctgcaagag cacagggcac ccacgtgctg gtccactgca agatgggcgt cagccgctca 1260
gcggccacag tgctggccta tgccatgaag cagtacgaat gcagcctgga gcaggccctg 1320
cgccacgtgc aggagctccg gcccatcgcc cgccccaacc ctggcttcct gcgccagctg 1380
cagatctacc agggcatcct gacggccaga acctga 1416

<210> 138
<211> 471
<212> PRT
<213> Mus musculus

<400> 138

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Met Ala Leu Val Thr Val Ser Arg Ser Pro Pro Gly Ser Gly Ala Ser
 1               5                  10                  15
Thr Pro Val Gly Pro Trp Asp Gln Ala Val Gln Arg Arg Ser Arg Leu
            20                  25                  30
Gln Arg Arg Gln Ser Phe Ala Val Leu Arg Gly Ala Val Leu Gly Leu
        35                  40                  45
Gln Asp Gly Gly Asp Asn Asp Asp Ala Ala Glu Ala Ser Ser Glu Pro
    50                  55                  60
Thr Glu Lys Ala Pro Ser Glu Glu Glu Leu His Gly Asp Gln Thr Asp
65                  70                  75                  80
Phe Gly Gln Gly Ser Gln Ser Pro Gln Lys Gln Glu Glu Gln Arg Gln
                85                  90                  95
His Leu His Leu Met Val Gln Leu Leu Arg Pro Gln Asp Asp Ile Arg
            100                 105                 110
Leu Ala Ala Gln Leu Glu Ala Pro Arg Pro Pro Arg Leu Arg Tyr Leu
        115                 120                 125
Leu Val Val Ser Thr Arg Glu Gly Glu Gly Leu Ser Gln Asp Glu Thr
    130                 135                 140
Val Leu Leu Gly Val Asp Phe Pro Asp Ser Ser Ser Pro Ser Cys Thr
145                 150                 155                 160
Leu Gly Leu Val Leu Pro Leu Trp Ser Asp Thr Gln Val Tyr Leu Asp
                165                 170                 175
Gly Asp Gly Gly Phe Ser Val Thr Ser Gly Gly Gln Ser Arg Ile Phe
            180                 185                 190
Lys Pro Ile Ser Ile Gln Thr Met Trp Ala Thr Leu Gln Val Leu His
        195                 200                 205
Gln Ala Cys Glu Ala Ala Leu Gly Ser Gly Leu Val Pro Gly Gly Ser
    210                 215                 220
```

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Ala Leu Thr Trp Ala Ser His Tyr Gln Glu Arg Leu Asn Ser Glu Gln
225                 230                 235                 240
Ser Cys Leu Asn Glu Trp Thr Ala Met Ala Asp Leu Glu Ser Leu Arg
                245                 250                 255
Pro Pro Ser Ala Glu Pro Gly Gly Ser Ser Glu Gln Glu Gln Met Glu
            260                 265                 270
Gln Ala Ile Arg Ala Glu Leu Trp Lys Val Leu Asp Val Ser Asp Leu
        275                 280                 285
Glu Ser Val Thr Ser Lys Glu Ile Arg Gln Ala Leu Glu Leu Arg Leu
    290                 295                 300
Gly Leu Pro Leu Gln Gln Tyr Arg Asp Phe Ile Asp Asn Gln Met Leu
305                 310                 315                 320
Leu Leu Val Ala Gln Arg Asp Arg Ala Ser Arg Ile Phe Pro His Leu
                325                 330                 335
Tyr Leu Gly Ser Glu Trp Asn Ala Ala Asn Leu Glu Glu Leu Gln Arg
            340                 345                 350
Asn Arg Val Thr His Ile Leu Asn Met Ala Arg Glu Ile Asp Asn Phe
        355                 360                 365
Tyr Pro Glu Arg Phe Thr Tyr His Asn Val Arg Leu Trp Asp Glu Glu
    370                 375                 380
Ser Ala Gln Leu Leu Pro His Trp Lys Glu Thr His Arg Phe Ile Glu
385                 390                 395                 400
Ala Ala Arg Ala Gln Gly Thr His Val Leu Val His Cys Lys Met Gly
                405                 410                 415
Val Ser Arg Ser Ala Ala Thr Val Leu Ala Tyr Ala Met Lys Gln Tyr
            420                 425                 430
Glu Cys Ser Leu Glu Gln Ala Leu Arg His Val Gln Glu Leu Arg Pro
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<210> 139
<211> 3496
<212> DNA
<213> Homo sapiens

<400> 139

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<211> 665
<212> PRT
<213> Homo sapiens

<400> 140
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Pro Phe Val Glu Tyr Asn Thr Ser His Ile Leu Glu Ala Ile Asn Ile
        35   40   45
Asn Cys Ser Lys Leu Met Lys Arg Arg Leu Gln Gln Asp Lys Val Leu
    50   55   60
Ile Thr Glu Leu Ile Gln His Ser Ala Lys His Lys Val Asp Ile Asp
65   70   75   80

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Cys Ser Gln Lys Val Val Val Tyr Asp Gln Ser Ser Gln Asp Val Ala
                85                  90                  95
Ser Leu Ser Ser Asp Cys Phe Leu Thr Val Leu Leu Gly Lys Leu Glu
            100                 105                 110
Lys Ser Phe Asn Ser Val His Leu Leu Ala Gly Gly Phe Ala Glu Phe
        115                 120                 125
Ser Arg Cys Phe Pro Gly Leu Cys Glu Gly Lys Ser Thr Leu Val Pro
    130                 135                 140
Thr Cys Ile Ser Gln Pro Cys Leu Pro Val Ala Asn Ile Gly Pro Thr
145                 150                 155                 160
Arg Ile Leu Pro Asn Leu Tyr Leu Gly Cys Gln Arg Asp Val Leu Asn
                165                 170                 175
Lys Glu Leu Met Gln Gln Asn Gly Ile Gly Tyr Val Leu Asn Ala Ser
            180                 185                 190
Asn Thr Cys Pro Lys Pro Asp Phe Ile Pro Glu Ser His Phe Leu Arg
        195                 200                 205
Val Pro Val Asn Asp Ser Phe Cys Glu Lys Ile Leu Pro Trp Leu Asp
    210                 215                 220
Lys Ser Val Asp Phe Ile Glu Lys Ala Lys Ala Ser Asn Gly Cys Val
225                 230                 235                 240
Leu Val His Cys Leu Ala Gly Ile Ser Arg Ser Ala Thr Ile Ala Ile
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Ala Tyr Ile Met Lys Arg Met Asp Met Ser Leu Asp Glu Ala Tyr Arg
            260                 265                 270
Phe Val Lys Glu Lys Arg Pro Thr Ile Ser Pro Asn Phe Asn Phe Leu
        275                 280                 285
Gly Gln Leu Leu Asp Tyr Glu Lys Lys Ile Lys Asn Gln Thr Gly Ala
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Ser Gly Pro Lys Ser Lys Leu Lys Leu Leu His Leu Glu Lys Pro Asn
305                 310                 315                 320
Glu Pro Val Pro Ala Val Ser Glu Gly Gly Gln Lys Ser Glu Thr Pro
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Leu Ser Pro Pro Cys Ala Asp Ser Ala Thr Ser Glu Ala Ala Gly Gln
            340                 345                 350
Arg Pro Val His Pro Ala Ser Val Pro Ser Val Pro Ser Val Gln Pro
        355                 360                 365
Ser Leu Leu Glu Asp Ser Pro Leu Val Gln Ala Leu Ser Gly Leu His
    370                 375                 380
Leu Ser Ala Asp Arg Leu Glu Asp Ser Asn Lys Leu Lys Arg Ser Phe
385                 390                 395                 400
Ser Leu Asp Ile Lys Ser Val Ser Tyr Ser Ala Ser Met Ala Ala Ser
                405                 410                 415
Leu His Gly Phe Ser Ser Ser Glu Asp Ala Leu Glu Tyr Tyr Lys Pro
            420                 425                 430
Ser Thr Thr Leu Asp Gly Thr Asn Lys Leu Cys Gln Phe Ser Pro Val
        435                 440                 445
Gln Glu Leu Ser Glu Gln Thr Pro Glu Thr Ser Pro Asp Lys Glu Glu
    450                 455                 460
Ala Ser Ile Pro Lys Lys Leu Gln Thr Ala Arg Pro Ser Asp Ser Gln
465                 470                 475                 480
Ser Lys Arg Leu His Ser Val Arg Thr Ser Ser Ser Gly Thr Ala Gln
                485                 490                 495
Arg Ser Leu Leu Ser Pro Leu His Arg Ser Gly Ser Val Glu Asp Asn
            500                 505                 510
Tyr His Thr Ser Phe Leu Phe Gly Leu Ser Thr Ser Gln Gln His Leu
        515                 520                 525
Thr Lys Ser Ala Gly Leu Gly Leu Lys Gly Trp His Ser Asp Ile Leu
    530                 535                 540
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Thr Glu Ser Ser His Phe Tyr Ser Ala Ser Ala Ile Tyr Gly Gly Ser
565 570 575
Ala Ser Tyr Ser Ala Tyr Ser Cys Ser Gln Leu Pro Thr Cys Gly Asp
580 585 590
Gln Val Tyr Ser Val Arg Arg Arg Gln Lys Pro Ser Asp Arg Ala Asp
595 600 605
Ser Arg Arg Ser Trp His Glu Glu Ser Pro Phe Glu Lys Gln Phe Lys
610 615 620
Arg Arg Ser Cys Gln Met Glu Phe Gly Glu Ser Ile Met Ser Glu Asn
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<210> 141
<211> 3332
<212> DNA
<213> Homo sapiens

<400> 141
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<210> 142
<211> 517
<212> PRT
<213> Homo sapiens

<400> 142
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Gln Gln Asn Gly Ile Gly Tyr Val Leu Asn Ala Ser Asn Thr Cys Pro
35 40 45
Lys Pro Asp Phe Ile Pro Glu Ser His Phe Leu Arg Val Pro Val Asn
50 55 60
Asp Ser Phe Cys Glu Lys Ile Leu Pro Trp Leu Asp Lys Ser Val Asp
65 70 75 80
Phe Ile Glu Lys Ala Lys Ala Ser Asn Gly Cys Val Leu Val His Cys
85 90 95
Leu Ala Gly Ile Ser Arg Ser Ala Thr Ile Ala Ile Ala Tyr Ile Met
100 105 110
Lys Arg Met Asp Met Ser Leu Asp Glu Ala Tyr Arg Phe Val Lys Glu
115 120 125
Lys Arg Pro Thr Ile Ser Pro Asn Phe Asn Phe Leu Gly Gln Leu Leu
130 135 140
Asp Tyr Glu Lys Lys Ile Lys Asn Gln Thr Gly Ala Ser Gly Pro Lys
145 150 155 160
Ser Lys Leu Lys Leu Leu His Leu Glu Lys Pro Asn Glu Pro Val Pro
165 170 175
Ala Val Ser Glu Gly Gly Gln Lys Ser Glu Thr Pro Leu Ser Pro Pro
180 185 190
Cys Ala Asp Ser Ala Thr Ser Glu Ala Ala Gly Gln Arg Pro Val His
195 200 205
Pro Ala Ser Val Pro Ser Val Pro Ser Val Gln Pro Ser Leu Leu Glu
210 215 220
Asp Ser Pro Leu Val Gln Ala Leu Ser Gly Leu His Leu Ser Ala Asp

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Arg Leu Glu Asp Ser Asn Lys Leu Lys Arg Ser Phe Ser Leu Asp Ile
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Lys Ser Val Ser Tyr Ser Ala Ser Met Ala Ala Ser Leu His Gly Phe
            260                 265                 270
Ser Ser Ser Glu Asp Ala Leu Glu Tyr Tyr Lys Pro Ser Thr Thr Leu
        275                 280                 285
Asp Gly Thr Asn Lys Leu Cys Gln Phe Ser Pro Val Gln Glu Leu Ser
    290                 295                 300
Glu Gln Thr Pro Glu Thr Ser Pro Asp Lys Glu Glu Ala Ser Ile Pro
305                 310                 315                 320
Lys Lys Leu Gln Thr Ala Arg Pro Ser Asp Ser Gln Ser Lys Arg Leu
                325                 330                 335
His Ser Val Arg Thr Ser Ser Ser Gly Thr Ala Gln Arg Ser Leu Leu
            340                 345                 350
Ser Pro Leu His Arg Ser Gly Ser Val Glu Asp Asn Tyr His Thr Ser
        355                 360                 365
Phe Leu Phe Gly Leu Ser Thr Ser Gln Gln His Leu Thr Lys Ser Ala
    370                 375                 380
Gly Leu Gly Leu Lys Gly Trp His Ser Asp Ile Leu Ala Pro Gln Thr
385                 390                 395                 400
Ser Thr Pro Ser Leu Thr Ser Ser Trp Tyr Phe Ala Thr Glu Ser Ser
                405                 410                 415
His Phe Tyr Ser Ala Ser Ala Ile Tyr Gly Gly Ser Ala Ser Tyr Ser
            420                 425                 430
Ala Tyr Ser Cys Ser Gln Leu Pro Thr Cys Gly Asp Gln Val Tyr Ser
        435                 440                 445
Val Arg Arg Arg Gln Lys Pro Ser Asp Arg Ala Asp Ser Arg Arg Ser
    450                 455                 460
Trp His Glu Glu Ser Pro Phe Glu Lys Gln Phe Lys Arg Arg Ser Cys
465                 470                 475                 480
Gln Met Glu Phe Gly Glu Ser Ile Met Ser Glu Asn Arg Ser Arg Glu
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<210> 143
<211> 1754
<212> DNA
<213> Homo sapiens

<400> 143

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<210> 144
<211> 188
<212> PRT
<213> Homo sapiens

<400> 144

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			20					25					30		
Ser	Ser	Cys	Ser	Arg	Val	Asp	Glu	Val	Trp	Pro	Asn	Leu	Phe	Ile	Gly
		35					40					45			
Asp	Ala	Ala	Thr	Ala	Asn	Asn	Arg	Phe	Glu	Leu	Trp	Lys	Leu	Gly	Ile
	50					55					60				
Thr	His	Val	Leu	Asn	Ala	Ala	His	Lys	Gly	Leu	Tyr	Cys	Gln	Gly	Gly
65					70					75					80
Pro	Asp	Phe	Tyr	Gly	Ser	Ser	Val	Ser	Tyr	Leu	Gly	Val	Pro	Ala	His
				85					90					95	
Asp	Leu	Pro	Asp	Phe	Asp	Ile	Ser	Ala	Tyr	Phe	Ser	Ser	Ala	Ala	Asp
			100					105					110		
Phe	Ile	His	Arg	Ala	Leu	Asn	Thr	Pro	Gly	Ala	Lys	Val	Leu	Val	His
		115					120					125			
Cys	Val	Val	Gly	Val	Ser	Arg	Ser	Ala	Thr	Leu	Val	Leu	Ala	Tyr	Leu
	130					135					140				
Met	Leu	His	Gln	Arg	Leu	Ser	Leu	Arg	Gln	Ala	Val	Ile	Thr	Val	Arg
145					150					155					160
Gln	His	Arg	Trp	Val	Phe	Pro	Asn	Arg	Gly	Phe	Leu	His	Gln	Leu	Cys
				165					170					175	
Arg	Leu	Asp	Gln	Gln	Leu	Arg	Gly	Ala	Gly	Gln	Ser				
			180					185							

<210> 145
<211> 1666
<212> DNA
<213> Homo sapiens

<400> 145
ggcccccgt tccccgccag gctgcaggcg tcgggcctgg gccgtcaggg cagctgtgac 60
cggatcgctt cccgggcggc gagctggggg tgcacccgga ccgccgcccc cgggatcatg 120

ggcaatggca tgaccaaggt acttcctgga ctctacctcg gaaacttcat tgatgccaaa 180
gacctggatc agctgggccg aaataagatc acacacatca tctctatcca tgagtcaccc 240
cagcctctgc tgcaggatat cacctacctt cgcatcccgg tcgctgatac ccctgaggta 300
cccatcaaaa agcacttcaa agaatgtatc aacttcatcc actgctgccg ccttaatggg 360
gggaactgcc ttgtgcactg ctttgcaggc atctctcgca gcaccacgat tgtgacagcg 420
tatgtgatga ctgtgacggg gctaggctgg cgggacgtgc ttgaagccat caaggccacc 480
aggcccatcg ccaaccccaa cccaggcttt aggcagcagc ttgaagagtt tggctgggcc 540
agttcccaga agggtgccag acataggacc tcaaaaacct ctggtgccca atgccctccg 600
atgacttcag caacctggat ggtcaccgga cccaaagtac cagatctgtc tgtgcttcgg 660
tgaggaggac ccgggcccca cacagcaccc caaggagcag ctcatcatgg cggacgtgca 720
ggtgcagctt cggcctggga gctcgtcctg cactctaagt gcctcaaccg agcgcccaga 780
tgggtcctca acccctggca accccgatgg catcactcac cttcaatgca gctgcctcca 840
tcctaagcga gccgcttcct cttcttgtac ccgctgaagg cagcccccaa caggggggct 900
ccctactccc acccaaccct gcccacacta agcccataga cttggggcct cccccggcac 960
atcacccagg tctgccggac ggcagaggtg gatcgcggcc ttccactcct ctgtcacggg 1020
gccccggaac tcgagagtag gccacaccgc cccccagctg ggcatggggc ttcggcagga 1080
aactgaactt gatcttgagg ccccagaaag gcagcaactg gagcagaagc aagacttcat 1140
ctcttgctga cagcccaatt tgtcaatagc gctttcctca gagccagcct taacctgctg 1200
ttgagtccat taaaacgttt gcttaaagtt tttaccaata attagatcat cagggttgtt 1260
tagtgtggga tcaagccata acaaaactgc ctagcctctc aggggcctag aatttacaga 1320
accttcctcc tccctgcagc aagtctctct tctttattct gggggctggg aaggatccca 1380
aaacagggaa cttggccgaa ccctgggctt tggatgctaa ccactgaagt accagcacct 1440
gtaggatgct gtctttgaag aaactgaggc ggacctccaa atgcagccct aaggcagagg 1500
tcaacgtgga agaccagccc ttctccaagc cccactggtc tttgcaagct gtacgttgta 1560
ggcaatctga gaactggaaa gggggactac aaccagaaag ttggttaccc tgccatggga 1620
ataaagtagc tgttttccac cccaaaaaaa aaaaaaaaaa aaaaaa 1666

<210> 146
<211> 181
<212> PRT
<213> Homo sapiens

<400> 146

```
Met Gly Asn Gly Met Thr Lys Val Leu Pro Gly Leu Tyr Leu Gly Asn
 1               5                  10                  15
Phe Ile Asp Ala Lys Asp Leu Asp Gln Leu Gly Arg Asn Lys Ile Thr
            20                  25                  30
His Ile Ile Ser Ile His Glu Ser Pro Gln Pro Leu Leu Gln Asp Ile
        35                  40                  45
Thr Tyr Leu Arg Ile Pro Val Ala Asp Thr Pro Glu Val Pro Ile Lys
    50                  55                  60
Lys His Phe Lys Glu Cys Ile Asn Phe Ile His Cys Cys Arg Leu Asn
65                  70                  75                  80
Gly Gly Asn Cys Leu Val His Cys Phe Ala Gly Ile Ser Arg Ser Thr
                85                  90                  95
Thr Ile Val Thr Ala Tyr Val Met Thr Val Thr Gly Leu Gly Trp Arg
            100                 105                 110
Asp Val Leu Glu Ala Ile Lys Ala Thr Arg Pro Ile Ala Asn Pro Asn
        115                 120                 125
Pro Gly Phe Arg Gln Gln Leu Glu Glu Phe Gly Trp Ala Ser Ser Gln
    130                 135                 140
Lys Gly Ala Arg His Arg Thr Ser Lys Thr Ser Gly Ala Gln Cys Pro
145                 150                 155                 160
Pro Met Thr Ser Ala Thr Trp Met Val Thr Gly Pro Lys Val Pro Asp
                165                 170                 175
Leu Ser Val Leu Arg
            180
```

<210> 147
<211> 1807
<212> DNA
<213> Homo sapiens

<400> 147
ggcccccgt tccccgccag gctgcaggcg tcgggcctgg gccgtcaggg cagctgtgac 60
cggatcgctt cccgggcggc gagctggggg tgcacccgga ccgccgcccc cgggatcatg 120
ggcaatggca tgaccaaggt acttcctgga ctctacctcg gaaacttcat tgatgccaaa 180
gacctggatc agctgggccg aaataagatc acacacatca tctctatcca tgagtcaccc 240
cagcctctgc tgcaggatat cacctacctt cgcatcccgg tcgctgatac ccctgaggta 300
cccatcaaaa agcacttcaa agaatgtatc aacttcatcc actgctgccg ccttaatggg 360
gggaactgcc ttgtgcactg ctttgcaggc atctctcgca gcaccacgat tgtgacagcg 420
tatgtgatga ctgtgacggg gctaggctgg cgggacgtgc ttgaagccat caaggccacc 480
aggcccatcg ccaaccccaa cccaggcttt aggcagcagc ttgaagagtt tggctgggcc 540
agttcccaga agggtgccag acataggacc tcaaaaacct ctggtgccca atgccctccg 600
atgacttcag caacctgcct gctggctgca cgtgtggctc ttctctccgc agcgctggtg 660
cgcgaagcca ccgggcgcac agcccagcgc tgtcgtctga gtccgcgggc ggccgccgag 720
cgcctgctgg ggccgccacc tcacgttgca gcaggatggt caccggaccc aaagtaccag 780
atctgtctgt gcttcggtga ggaggacccg ggccccacac agcaccccaa ggagcagctc 840
atcatggcgg acgtgcaggt gcagcttcgg cctgggagct cgtcctgcac tctaagtgcc 900
tcaaccgagc gcccagatgg gtcctcaacc cctggcaacc ccgatggcat cactcacctt 960
caatgcagct gcctccatcc taagcgagcc gcttcctctt cttgtacccg ctgaaggcag 1020
cccccaacag gggggctccc tactcccacc caaccctgcc cacactaagc ccatagactt 1080
ggggcctccc cggcggcaca tcacccaggt ctgccggacg gcagaggtgg atcgcggcct 1140
tccactcctc tgtcacgggg ccccggaact cgagagtagg ccacaccgcc ccccagctgg 1200
gcatggggct tcggcaggaa actgaacttg atcttgaggc cccagaaagg cagcaactgg 1260
agcagaagca agacttcatc tcttgctgac agcccaattt gtcaatagcg ctttcctcag 1320
agccagcctt aacctgctgt tgagtccatt aaaacgtttg cttaaagttt ttaccaataa 1380
ttagatcatc agggttgttt agtgtgggat caagccataa caaaactgcc tagcctctca 1440
ggggcctaga atttacagaa ccttcctcct ccctgcagct agtctctctt ctttattctg 1500
ggggctggga aggatcccaa aacagggaac ttggccgaac cctgggcttt ggatgctaac 1560
cactgaagta ccagcacctg taggatgctg tctttgaaga aactgaggcg gacctccaaa 1620
tgcagcccta aggcagaggt caacgtggaa gaccagccct tctccaagcc ccactggtct 1680
ttgcaagctg tacgttgtag gcaatctgag aactggaaag ggggactaca accagaaagt 1740
tggttaccct gccatgggaa taaagtagct gttttccacc ccaaaaaaaa aaaaaaaaaa 1800
aaaaaaa 1807

<210> 148
<211> 298
<212> PRT
<213> Homo sapiens

<400> 148
Met Gly Asn Gly Met Thr Lys Val Leu Pro Gly Leu Tyr Leu Gly Asn
1 5 10 15
Phe Ile Asp Ala Lys Asp Leu Asp Gln Leu Gly Arg Asn Lys Ile Thr
20 25 30
His Ile Ile Ser Ile His Glu Ser Pro Gln Pro Leu Leu Gln Asp Ile
35 40 45
Thr Tyr Leu Arg Ile Pro Val Ala Asp Thr Pro Glu Val Pro Ile Lys
50 55 60
Lys His Phe Lys Glu Cys Ile Asn Phe Ile His Cys Cys Arg Leu Asn
65 70 75 80
Gly Gly Asn Cys Leu Val His Cys Phe Ala Gly Ile Ser Arg Ser Thr
85 90 95
Thr Ile Val Thr Ala Tyr Val Met Thr Val Thr Gly Leu Gly Trp Arg

```
            100                 105                 110
Asp Val Leu Glu Ala Ile Lys Ala Thr Arg Pro Ile Ala Asn Pro Asn
        115                 120                 125
Pro Gly Phe Arg Gln Gln Leu Glu Glu Phe Gly Trp Ala Ser Ser Gln
    130                 135                 140
Lys Gly Ala Arg His Arg Thr Ser Lys Thr Ser Gly Ala Gln Cys Pro
145                 150                 155                 160
Pro Met Thr Ser Ala Thr Cys Leu Leu Ala Ala Arg Val Ala Leu Leu
                165                 170                 175
Ser Ala Ala Leu Val Arg Glu Ala Thr Gly Arg Thr Ala Gln Arg Cys
            180                 185                 190
Arg Leu Ser Pro Arg Ala Ala Ala Glu Arg Leu Leu Gly Pro Pro Pro
        195                 200                 205
His Val Ala Ala Gly Trp Ser Pro Asp Pro Lys Tyr Gln Ile Cys Leu
    210                 215                 220
Cys Phe Gly Glu Glu Asp Pro Gly Pro Thr Gln His Pro Lys Glu Gln
225                 230                 235                 240
Leu Ile Met Ala Asp Val Gln Val Gln Leu Arg Pro Gly Ser Ser Ser
                245                 250                 255
Cys Thr Leu Ser Ala Ser Thr Glu Arg Pro Asp Gly Ser Ser Thr Pro
            260                 265                 270
Gly Asn Pro Asp Gly Ile Thr His Leu Gln Cys Ser Cys Leu His Pro
        275                 280                 285
Lys Arg Ala Ala Ser Ser Ser Cys Thr Arg
    290                 295
```

<210> 149
<211> 1268
<212> DNA
<213> Homo sapiens

<400> 149

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ggcccccgt tccccgccag gctgcaggcg tcgggcctgg gccgtcaggg cagctgtgac 60
cggatcgctt cccgggcggc gagctggggg tgcacccgga ccgccgcccc cgggatcatg 120
ggcaatggca tgaccaaggt acttcctgga ctctacctcg gaaacttcat tgatgccaaa 180
gacctggatc agctgggccg aaataagatc acacacatca tctctatcca tgagtcaccc 240
cagcctctgc tgcaggatat cacctacctt cgcatcccgg tcgctgatac ccctgaggta 300
cccatcaaaa agcacttcaa agaatgtatc aacttcatcc actgctgccg ccttaatggg 360
gggaactgcc ttgtgcactg ctttgcaggc atctctcgca gcaccacgat tgtgacagcg 420
tatgtgatga ctgtgacggg gctaggctgg cgggacgtgc ttgaagccat caaggccacc 480
aggcccatcg ccaaccccaa cccaggcttt aggcagcagc ttgaagagtt tggctgggcc 540
agttcccaga agggtgccag acataggacc tcaaaaacct ctggtgccca atgccctccg 600
atgacttcag caacctggat ggtcaccgga cccaaagtac cagatctgtc tgtgcttcgg 660
tgaggaggac ccgggcccca cacagcaccc caaggagcag ctcatcatgg cggacgtgca 720
ggtgcagctt cggcctggga gctcgtcctg cactctaagt gcctcaaccg agcgcccaga 780
tgggtcctca acccctggca accccgatgg catcactcac cttcaatgca gcttgcctcc 840
atcctaagcg agccgcttcc tcttcttgta cccgctgaag gcaagccccc aacaggggg 900
ctccctactc ccacccaacc ctgcccacac taagcccata gacttggggc ctccccggc 960
acatcaccca ggtctgccgg acggcagagg tggatcgcgg ccttccactc ctctgtcacg 1020
gggccccgga actcgagagt aggcctcacc gccccccagc tgggcatggg gcttcggcag 1080
gaaactgaac ttgatcttga ggccagcaga aaggcagcaa ctggagcaga agcaagactt 1140
catctcttgc tgacagccca atttgtcaat agcgctttcc tcagagccag ccttaacctg 1200
ctgttgagtc cattaaaacg tttgcttaaa gtttttacca ataaaaaaaa aaaaaaaaaa 1260
aaaaaaaa                                                          1268
```

<210> 150
<211> 181

<212> PRT
<213> Homo sapiens

<400> 150

```
Met Gly Asn Gly Met Thr Lys Val Leu Pro Gly Leu Tyr Leu Gly Asn
 1               5                  10                  15
Phe Ile Asp Ala Lys Asp Leu Asp Gln Leu Gly Arg Asn Lys Ile Thr
            20                  25                  30
His Ile Ile Ser Ile His Glu Ser Pro Gln Pro Leu Leu Gln Asp Ile
        35                  40                  45
Thr Tyr Leu Arg Ile Pro Val Ala Asp Thr Pro Glu Val Pro Ile Lys
    50                  55                  60
Lys His Phe Lys Glu Cys Ile Asn Phe Ile His Cys Cys Arg Leu Asn
65                  70                  75                  80
Gly Gly Asn Cys Leu Val His Cys Phe Ala Gly Ile Ser Arg Ser Thr
                85                  90                  95
Thr Ile Val Thr Ala Tyr Val Met Thr Val Thr Gly Leu Gly Trp Arg
            100                 105                 110
Asp Val Leu Glu Ala Ile Lys Ala Thr Arg Pro Ile Ala Asn Pro Asn
        115                 120                 125
Pro Gly Phe Arg Gln Gln Leu Glu Glu Phe Gly Trp Ala Ser Ser Gln
    130                 135                 140
Lys Gly Ala Arg His Arg Thr Ser Lys Thr Ser Gly Ala Gln Cys Pro
145                 150                 155                 160
Pro Met Thr Ser Ala Thr Trp Met Val Thr Gly Pro Lys Val Pro Asp
                165                 170                 175
Leu Ser Val Leu Arg
            180
```

<210> 151
<211> 1045
<212> DNA
<213> Homo sapiens

<400> 151

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ggcccccgt tccccgccag gctgcaggcg tcgggcctgg gccgtcaggg cagctgtgac 60
cggatcgctt cccgggcggc gagctggggg tgcacccgga ccgccgcccc cgggatcatg 120
ggcaatggca tgaccaaggt acttcctgga ctctacctcg gaaacttcat tgatgccaaa 180
gacctggatc agctgggccg aaataagatc acacacatca tctctatcca tgagtcaccc 240
cagcctctgc tgcaggatat cacctacctt cgcatcccgg tcgctgatac ccctgaggta 300
cccatcaaaa agcacttcaa agaatgtatc aacttcatcc actgctgccg ccttaatggg 360
gggaactgcc ttgtgcactg ctttgcaggc atctctcgca gcaccacgat tgtgacagcg 420
tatgtgatga ctgtgacggg gctaggctgg cgggacgtgc ttgaagccat caaggccacc 480
aggcccatcg ccaaccccaa cccaggcttt aggcagcagc ttgaagagtt tggctgggcc 540
agttcccaga agggtgccag acataggacc tcaaaaacct ctggtgccca atgccctccg 600
atgacttcag caacctggat ggtcaccgga cccaaagtac cagatctgtc tgtgcttcgg 660
tgaggaggac ccgggcccca cacagcaccc caaggagcag ctcatcatgg cggacctagt 720
ctctcttctt tattctgggg gctgggaagg atcccaaaac agggaacttg gccgaaccct 780
gggctttgga tgctaaccac tgaagtacca gcacctgtag gatgctgtct ttgaagaaac 840
tgaggcggac ctccaaatgc agccctaagg cagaggtcaa cgtggaagac cagcccttct 900
ccaagcccca ctggtctttg caagctgtac gttgtaggca atctgagaac tggaaagggg 960
gactacaacc agaaagttgg ttaccctgcc atgggaataa agtagctgtt ttccacccca 1020
taaaaaaaaa aaaaaaaaaa aaaaa                                      1045
```

<210> 152
<211> 181
<212> PRT

<213> Homo sapiens

<400> 152

```
Met Gly Asn Gly Met Thr Lys Val Leu Pro Gly Leu Tyr Leu Gly Asn
 1               5                  10                  15
Phe Ile Asp Ala Lys Asp Leu Asp Gln Leu Gly Arg Asn Lys Ile Thr
            20                  25                  30
His Ile Ile Ser Ile His Glu Ser Pro Gln Pro Leu Leu Gln Asp Ile
        35                  40                  45
Thr Tyr Leu Arg Ile Pro Val Ala Asp Thr Pro Glu Val Pro Ile Lys
    50                  55                  60
Lys His Phe Lys Glu Cys Ile Asn Phe Ile His Cys Cys Arg Leu Asn
65                  70                  75                  80
Gly Gly Asn Cys Leu Val His Cys Phe Ala Gly Ile Ser Arg Ser Thr
                85                  90                  95
Thr Ile Val Thr Ala Tyr Val Met Thr Val Thr Gly Leu Gly Trp Arg
            100                 105                 110
Asp Val Leu Glu Ala Ile Lys Ala Thr Arg Pro Ile Ala Asn Pro Asn
        115                 120                 125
Pro Gly Phe Arg Gln Gln Leu Glu Glu Phe Gly Trp Ala Ser Ser Gln
    130                 135                 140
Lys Gly Ala Arg His Arg Thr Ser Lys Thr Ser Gly Ala Gln Cys Pro
145                 150                 155                 160
Pro Met Thr Ser Ala Thr Trp Met Val Thr Gly Pro Lys Val Pro Asp
                165                 170                 175
Leu Ser Val Leu Arg
            180
```

<210> 153
<211> 982
<212> DNA
<213> Homo sapiens

<400> 153

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ggcccccgt tccccgccag gctgcaggcg tcgggcctgg gccgtcaggg cagctgtgac 60
cggatcgctt cccgggcggc gagctggggg tgcacccgga ccgccgcccc cgggatcatg 120
ggcaatggca tgaccaaggt acttcctgga ctctacctcg gaaacttcat tgatgccaaa 180
gacctggatc agctgggccg aaataagatc acacacatca tctctatcca tgagtcaccc 240
cagcctctgc tgcaggatat cacctacctt cgcatcccgg tcgctgatac ccctgaggta 300
cccatcaaaa agcacttcaa agaatgtatc aacttcatcc actgctgccg ccttaatggg 360
gggaactgcc ttgtgcactg ctttgcaggc atctctcgca gcaccacgat tgtgacagcg 420
tatgtgatga ctgtgacggg gctaggctgg cgggacgtgc ttgaagccat caaggccacc 480
aggcccatcg ccaaccccaa cccaggcttt aggcagcagc ttaagagttt ggctgggcca 540
gttcccagaa ggatggtcac cggacccaaa gtaccagatc tgtctgtgct tcggtgagga 600
ggacccgggc cccacacagc accccaagga gcagctcatc atggcggacc tagtctctct 660
tctttattct gggggctggg aaggatccca aaacagggaa cttggccgaa ccctgggctt 720
tggatgctaa ccactgaagt accagcacct gtaggatgct gtctttgaag aaactgaggc 780
ggacctccaa atgcagccct aaggcagagg tcaacgtgga agaccagccc ttctccaagc 840
cccactggtc tttgcaagct gtacgttgta ggcaatctga gaactggaaa gggggactac 900
aaccagaaag ttggttaccc tgccatggga ataaagtagc tgttttccac cccccaaaaa 960
aaaaaaaaaa aaaaaaaaaa aa                                          982
```

<210> 154
<211> 159
<212> PRT
<213> Homo sapiens

<400> 154
Met Gly Asn Gly Met Thr Lys Val Leu Pro Gly Leu Tyr Leu Gly Asn
1 5 10 15
Phe Ile Asp Ala Lys Asp Leu Asp Gln Leu Gly Arg Asn Lys Ile Thr
20 25 30
His Ile Ile Ser Ile His Glu Ser Pro Gln Pro Leu Leu Gln Asp Ile
35 40 45
Thr Tyr Leu Arg Ile Pro Val Ala Asp Thr Pro Glu Val Pro Ile Lys
50 55 60
Lys His Phe Lys Glu Cys Ile Asn Phe Ile His Cys Cys Arg Leu Asn
65 70 75 80
Gly Gly Asn Cys Leu Val His Cys Phe Ala Gly Ile Ser Arg Ser Thr
85 90 95
Thr Ile Val Thr Ala Tyr Val Met Thr Val Thr Gly Leu Gly Trp Arg
100 105 110
Asp Val Leu Glu Ala Ile Lys Ala Thr Arg Pro Ile Ala Asn Pro Asn
115 120 125
Pro Gly Phe Arg Gln Gln Leu Lys Ser Leu Ala Gly Pro Val Pro Arg
130 135 140
Arg Met Val Thr Gly Pro Lys Val Pro Asp Leu Ser Val Leu Arg
145 150 155

<210> 155
<211> 1064
<212> DNA
<213> Homo sapiens

<400> 155
ggcccccgt tccccgccag gctgcaggcg tcgggcctgg gccgtcaggg cagctgtgac 60
cggatcgctt cccgggcggc gagctggggg tgcacccgga ccgccgcccc cgggatcatg 120
ggcaatggca tgaccaaggt acttcctgga ctctacctcg gaaacttcat tgatgccaaa 180
gacctggatc agctgggccg aaataagatc acacacatca tctctatcca tgagtcaccc 240
cagcctctgc tgcaggatat cacctacctt cgcatcccgg tcgctgatac ccctgaggta 300
cccatcaaaa agcacttcaa agaatgtatc aacttcatcc actgctgccg ccttaatggg 360
gggaactgcc ttgtgcactg ctttgcaggc atctctcgca gcaccacgat tgtgacagcg 420
tatgtgatga ctgtgacggg gctaggctgg cgggacgtgc ttgaagccat caaggccacc 480
aggcccatcg ccaaccccaa cccaggcttt aggcagcagc ttgaagagtt tggctgggcc 540
agttcccaga agggctttta ccaacctcat aagctgttgt gagaaccaat tgagacactg 600
caggaaagtg tttagccagg cccagcactg atgagcagtc ggatggtcac cggacccaaa 660
gtaccagatc tgtctgtgct tcggtgagga ggacccgggc cccacacagc accccaagga 720
gcagctcatc atggcggacc tagtctctct tctttattct gggggctggg aaggatccca 780
aaacagggaa cttggccgaa ccctgggctt tggatgctaa ccactgaagt accagcacct 840
gtaggatgct gtctttgaag aaactgaggc ggacctccaa atgcagccct aaggcagagg 900
tcaacgtgga agaccagccc ttctccaagc cccactggtc tttgcaagct gtacgttgta 960
ggcaatctga gaactggaaa gggggactac aaccagaaag ttggttaccc tgccatggga 1020
ataaagtagc tgttttccaa aaaaaaaaaa aaaaaaaaaa aaaa 1064

<210> 156
<211> 154
<212> PRT
<213> Homo sapiens

<400> 156
Met Gly Asn Gly Met Thr Lys Val Leu Pro Gly Leu Tyr Leu Gly Asn
1 5 10 15
Phe Ile Asp Ala Lys Asp Leu Asp Gln Leu Gly Arg Asn Lys Ile Thr
20 25 30

```
His Ile Ile Ser Ile His Glu Ser Pro Gln Pro Leu Leu Gln Asp Ile
        35                  40                  45
Thr Tyr Leu Arg Ile Pro Val Ala Asp Thr Pro Glu Val Pro Ile Lys
    50                  55                  60
Lys His Phe Lys Glu Cys Ile Asn Phe Ile His Cys Cys Arg Leu Asn
65                  70                  75                  80
Gly Gly Asn Cys Leu Val His Cys Phe Ala Gly Ile Ser Arg Ser Thr
                85                  90                  95
Thr Ile Val Thr Ala Tyr Val Met Thr Val Thr Gly Leu Gly Trp Arg
            100                 105                 110
Asp Val Leu Glu Ala Ile Lys Ala Thr Arg Pro Ile Ala Asn Pro Asn
        115                 120                 125
Pro Gly Phe Arg Gln Gln Leu Glu Glu Phe Gly Trp Ala Ser Ser Gln
    130                 135                 140
Lys Gly Phe Tyr Gln Pro His Lys Leu Leu
145                 150
```

<210> 157
<211> 833
<212> DNA
<213> Homo sapiens

<400> 157

```
ggcccccccgt tccccgccag gctgcaggcg tcgggcctgg gccgtcaggg cagctgtgac 60
cggatcgctt cccgggcggc gagctggggg tgcacccgga ccgccgcccc cgggatcatg 120
ggcaatggca tgaccaaggt acttcctgga ctctacctcg gaaacttcat tgatgccaaa 180
gacctggatc agctgggccg aaataagatc acacacatca tctctatcca tgagtcaccc 240
cagcctctgc tgcaggatat cacctacctt cgcatcccgg tcgctgatac ccctgaggta 300
cccatcaaaa agcacttcaa agaatgtatc aacttcatcc actgctgccg ccttaatggg 360
gggaactgcc ttgtgcactg ctttgcaggc atctctcgca gcaccacgat tgtgacagcg 420
tatgtgatga ctgtgacggg gctaggctgg cgggacgtgc ttgaagccat caaggccacc 480
aggcccatcg ccaaccccaa cccaggcttt aggcagcagc ttgaagagtt tggctgggcc 540
agttcccaga agcttcgccg gcagctggag gagcgcttcg gcgagagccc cttccgcgac 600
gaggaggagt tgcgcgcgct gctgccgctg tgcaagcgct gccggcaggg ctccgcgacc 660
tcggcctcct ccgccgggcc gcactcagca gcctccgagg gaaccgtgca gcgcctggtg 720
ccgcgcacgc cccgggaagc ccaccggccg ctgccgctgc tggcgcgcgt caagcagact 780
ttctcttgcc tcccccggtg tctgtcccgc aagggcggca agtgaggatg cag         833
```

<210> 158
<211> 235
<212> PRT
<213> Homo sapiens

<400> 158

```
Met Gly Asn Gly Met Thr Lys Val Leu Pro Gly Leu Tyr Leu Gly Asn
 1               5                  10                  15
Phe Ile Asp Ala Lys Asp Leu Asp Gln Leu Gly Arg Asn Lys Ile Thr
            20                  25                  30
His Ile Ile Ser Ile His Glu Ser Pro Gln Pro Leu Leu Gln Asp Ile
        35                  40                  45
Thr Tyr Leu Arg Ile Pro Val Ala Asp Thr Pro Glu Val Pro Ile Lys
    50                  55                  60
Lys His Phe Lys Glu Cys Ile Asn Phe Ile His Cys Cys Arg Leu Asn
65                  70                  75                  80
Gly Gly Asn Cys Leu Val His Cys Phe Ala Gly Ile Ser Arg Ser Thr
                85                  90                  95
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Asp Glu Glu Glu Leu Arg Ala Leu Leu Pro Leu Cys Lys Arg Cys Arg
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Gln Gly Ser Ala Thr Ser Ala Ser Ser Ala Gly Pro His Ser Ala Ala
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145 150 155 160
Lys Thr Ile Thr Val Val His Gln Pro Trp Cys Asn Ile Thr Gly Leu
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Pro Gly Thr Arg Tyr Asn Ala Thr Val Tyr Ser Gln Ala Ala Asn Gly
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Val Phe Asp Val Thr Ala Val Asn Ile Ser Ala Thr Ser Leu Thr Leu
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385 390 395 400
Ile His Val Ala Gly Glu Thr Asp Ser Ser Asn Leu Asn Val Ser Glu
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465                 470                 475                 480
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                485                 490                 495
Glu Ile Thr Thr Asn Gln Ser Ile Ile Ile Gly Gly Leu Phe Pro Gly
            500                 505                 510
Thr Lys Tyr Cys Phe Glu Ile Val Pro Lys Gly Pro Asn Gly Thr Glu
        515                 520                 525
Gly Ala Ser Arg Thr Val Cys Asn Arg Thr Val Pro Ser Ala Val Phe
    530                 535                 540
Asp Ile His Val Val Tyr Val Thr Thr Thr Glu Met Trp Leu Asp Trp
545                 550                 555                 560
Lys Ser Pro Asp Gly Ala Ser Glu Tyr Val Tyr His Leu Val Ile Glu
                565                 570                 575
Ser Lys His Gly Ser Asn His Thr Ser Thr Tyr Asp Lys Ala Ile Thr
            580                 585                 590
Leu Gln Gly Leu Ile Pro Gly Thr Leu Tyr Asn Ile Thr Ile Ser Pro
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Glu Val Asp His Val Trp Gly Asp Pro Asn Ser Thr Ala Gln Tyr Thr
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Arg Pro Ser Asn Val Ser Asn Ile Asp Val Ser Thr Asn Thr Thr Ala
625                 630                 635                 640
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Tyr Cys Leu Leu Ile Glu Lys Ala Gly Asn Ser Ser Asn Ala Thr Gln
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Val Val Thr Asp Ile Gly Ile Thr Asp Ala Thr Val Thr Glu Leu Ile
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Pro Gly Ser Ser Tyr Thr Val Glu Leu Phe Ala Gln Val Gly Asp Gly
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Val Leu Lys Trp Thr Cys Pro Pro Gly Ala Asn Ala Gly Phe Glu Leu
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Glu Val Ser Ser Gly Ala Trp Asn Asn Ala Thr His Leu Glu Ser Cys
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Ser Ser Glu Asn Gly Thr Glu Tyr Arg Thr Glu Val Thr Tyr Leu Asn
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Pro Pro Pro Asp Gly Ser Pro Asn Ile Thr Ser Val Ser His Asn Ser
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Val Lys Val Lys Phe Ser Gly Phe Glu Ala Ser His Gly Pro Ile Lys
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Ala Tyr Ala Val Ile Leu Thr Thr Gly Glu Ala Gly His Pro Ser Ala
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Asp Val Leu Lys Tyr Thr Tyr Asp Asp Phe Lys Lys Gly Ala Ser Asp
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Thr Tyr Val Thr Tyr Leu Ile Arg Thr Glu Glu Lys Gly Arg Ser Gln
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Lys Gly Leu Ile Asp Gly Ala Glu Ser Tyr Val Ser Phe Ser Arg Tyr
945                 950                 955                 960
Ser Asp Ala Val Ser Leu Pro Gln Asp Pro Gly Val Ile Cys Gly Ala
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Val Phe Gly Cys Ile Phe Gly Ala Leu Val Ile Val Thr Val Gly Gly
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tgtttctcag gattcctaac gattcaaatt accgttgagt atatataaag aatcgagtcg 3840
gaagaacaaa tgtgtgcatt caccccccagt cacaatggtc tccattgcat ttcaaaggag 3900
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tgtattcatt ttgattgtcc taaa 3984

<210> 162
<211> 913
<212> PRT
<213> Homo sapiens

<400> 162

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Thr Ser Glu Leu Pro Lys Glu Lys Thr Arg Ser Glu Val Ile Cys Ser
            20                  25                  30
Ile His Phe Leu Asp Gly Val Val Gln Thr Phe Lys Val Thr Lys Gln
        35                  40                  45
Asp Thr Gly Gln Val Leu Leu Asp Met Val His Asn His Leu Gly Val
    50                  55                  60
Thr Glu Lys Glu Tyr Phe Gly Leu Gln His Asp Asp Asp Ser Val Asp
65                  70                  75                  80
Ser Pro Arg Trp Leu Glu Ala Ser Lys Pro Ile Arg Lys Gln Leu Lys
                85                  90                  95
Gly Gly Phe Pro Cys Thr Leu His Phe Arg Val Arg Phe Phe Ile Pro
            100                 105                 110
Asp Pro Asn Thr Leu Gln Gln Glu Gln Thr Arg His Leu Tyr Phe Leu
        115                 120                 125
Gln Leu Lys Met Asp Ile Cys Glu Gly Arg Leu Thr Cys Pro Leu Asn
    130                 135                 140
Ser Ala Val Val Leu Ala Ser Tyr Ala Val Gln Ser His Phe Gly Asp
145                 150                 155                 160
Tyr Asn Ser Ser Ile His His Pro Gly Tyr Leu Ser Asp Ser His Phe
                165                 170                 175
Ile Pro Asp Gln Asn Glu Asp Phe Leu Thr Lys Val Glu Ser Leu His
            180                 185                 190
Glu Gln His Ser Gly Leu Lys Gln Ser Glu Ala Glu Ser Cys Tyr Ile
        195                 200                 205
Asn Ile Ala Arg Thr Leu Asp Phe Tyr Gly Val Glu Leu His Ser Gly
    210                 215                 220
Arg Asp Leu His Asn Leu Asp Leu Met Ile Gly Ile Ala Ser Ala Gly
225                 230                 235                 240
Val Ala Val Tyr Arg Lys Tyr Ile Cys Thr Ser Phe Tyr Pro Trp Val
                245                 250                 255
Asn Ile Leu Lys Ile Ser Phe Lys Arg Lys Lys Phe Phe Ile His Gln
            260                 265                 270
Arg Gln Lys Gln Ala Glu Ser Arg Glu His Ile Val Ala Phe Asn Met
        275                 280                 285
```

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Leu Asn Tyr Arg Ser Cys Lys Asn Leu Trp Lys Ser Cys Val Glu His
    290                 295                 300
His Thr Phe Phe Gln Ala Lys Lys Leu Leu Pro Gln Glu Lys Asn Val
305                 310                 315                 320
Leu Ser Gln Tyr Trp Thr Met Gly Ser Arg Asn Thr Lys Lys Ser Val
                325                 330                 335
Asn Asn Gln Tyr Cys Lys Lys Val Ile Gly Gly Met Val Trp Asn Pro
            340                 345                 350
Ala Met Arg Arg Ser Leu Ser Val Glu His Leu Glu Thr Lys Ser Leu
        355                 360                 365
Pro Ser Arg Ser Pro Pro Ile Thr Pro Asn Trp Arg Ser Pro Arg Leu
    370                 375                 380
Arg His Glu Ile Arg Lys Pro Arg His Ser Ser Ala Asp Asn Leu Ala
385                 390                 395                 400
Asn Glu Met Thr Tyr Ile Thr Glu Thr Glu Asp Val Phe Tyr Thr Tyr
                405                 410                 415
Lys Gly Ser Leu Ala Pro Gln Asp Ser Asp Ser Glu Val Ser Gln Asn
            420                 425                 430
Arg Ser Pro His Gln Glu Ser Leu Ser Glu Asn Asn Pro Ala Gln Ser
        435                 440                 445
Tyr Leu Thr Gln Lys Ser Ser Ser Ser Val Ser Pro Ser Ser Asn Ala
    450                 455                 460
Pro Gly Ser Cys Ser Pro Asp Gly Val Asp Gln Gln Leu Leu Asp Asp
465                 470                 475                 480
Phe His Arg Val Thr Lys Gly Gly Ser Thr Glu Asp Ala Ser Gln Tyr
                485                 490                 495
Tyr Cys Asp Lys Asn Asp Asn Gly Asp Ser Tyr Leu Val Leu Ile Arg
            500                 505                 510
Ile Thr Pro Asp Glu Asp Gly Lys Phe Gly Phe Asn Leu Lys Gly Gly
        515                 520                 525
Val Asp Gln Lys Met Pro Leu Val Val Ser Arg Ile Asn Pro Glu Ser
    530                 535                 540
Pro Ala Asp Thr Cys Ile Pro Lys Leu Asn Glu Gly Asp Gln Ile Val
545                 550                 555                 560
Leu Ile Asn Gly Arg Asp Ile Ser Glu His Thr His Asp Gln Val Val
                565                 570                 575
Met Phe Ile Lys Ala Ser Arg Glu Ser His Ser Arg Glu Leu Ala Leu
            580                 585                 590
Val Ile Arg Arg Arg Ala Val Arg Ser Phe Ala Asp Phe Lys Ser Glu
        595                 600                 605
Asp Glu Leu Asn Gln Leu Phe Pro Glu Ala Ile Phe Pro Met Cys Pro
    610                 615                 620
Glu Gly Gly Asp Thr Leu Glu Gly Ser Met Ala Gln Leu Lys Lys Gly
625                 630                 635                 640
Leu Glu Ser Gly Thr Val Leu Ile Gln Phe Glu Gln Leu Tyr Arg Lys
                645                 650                 655
Lys Pro Gly Leu Ala Ile Thr Phe Ala Lys Leu Pro Gln Asn Leu Asp
            660                 665                 670
Lys Asn Arg Tyr Lys Asp Val Leu Pro Tyr Asp Thr Thr Arg Val Leu
        675                 680                 685
Leu Gln Gly Asn Glu Asp Tyr Ile Asn Ala Ser Tyr Val Asn Met Glu
    690                 695                 700
Ile Pro Ala Ala Asn Leu Val Asn Lys Tyr Ile Ala Thr Gln Gly Pro
705                 710                 715                 720
Leu Pro His Thr Cys Ala Gln Phe Trp Gln Val Val Trp Asp Gln Lys
                725                 730                 735
Leu Ser Leu Ile Val Met Leu Thr Thr Leu Thr Glu Arg Gly Arg Thr
            740                 745                 750
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Lys Cys His Gln Tyr Trp Pro Asp Pro Pro Asp Val Met Asn His Gly
        755                 760                 765
Gly Phe His Ile Gln Cys Gln Ser Glu Asp Cys Thr Ile Ala Tyr Val
    770                 775                 780
Ser Arg Glu Met Leu Val Thr Asn Thr Gln Thr Gly Glu Glu His Thr
785                 790                 795                 800
Val Thr His Leu Gln Tyr Val Ala Trp Pro Asp His Gly Ile Pro Asp
                805                 810                 815
Asp Ser Ser Asp Phe Leu Glu Phe Val Asn Tyr Val Arg Ser Leu Arg
            820                 825                 830
Val Asp Ser Glu Pro Val Leu Val His Cys Ser Ala Gly Ile Gly Arg
        835                 840                 845
Thr Gly Val Leu Val Thr Met Glu Thr Ala Met Cys Leu Thr Glu Arg
    850                 855                 860
Asn Leu Pro Ile Tyr Pro Leu Asp Ile Val Arg Lys Met Arg Asp Gln
865                 870                 875                 880
Arg Ala Met Met Val Gln Thr Ser Ser Gln Tyr Lys Phe Val Cys Glu
                885                 890                 895
Ala Ile Leu Arg Val Tyr Glu Glu Gly Leu Val Gln Met Leu Asp Pro
            900                 905                 910
Ser
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<210> 163
<211> 2287
<212> DNA
<213> Homo sapien

<400> 163

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ctgtacttgg aaattcgaaa tgagtcccat gactatcctc atagagtggc caagtttcca 180
gaaaacagaa atcgaaacag atacagagat gtaagcccat atgatcacag tcgtgttaaa 240
ctgcaaaatg ctgagaatga ttatattaat gccagtttag ttgacataga agaggcacaa 300
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gtttggcagc agaagaccaa agcagttgtc atgctgaacc gcattgtgga gaaagaatcg 420
gttaaatgtg cacagtactg gccaacagat gaccaagaga tgctgtttaa agaaacagga 480
ttcagtgtga agctcttgtc agaagatgtg aagtcgtatt atacagtaca tctactacaa 540
ttagaaaata tcaatagtgg tgaaaccaga acaatatctc actttcatta tactacctgg 600
ccagattttg gagtccctga atcaccagct tcatttctca atttcttgtt taaagtgaga 660
gaatctggct ccttgaaccc tgaccatggg cctgcggtga tccactgtag tgcaggcatt 720
gggcgctctg gcaccttctc tctggtagac acttgtcttg ttttgatgga aaaaggagat 780
gatattaaca taaaacaagt gttactgaac atgagaaaat accgaatggg tcttattcag 840
accccagatc aactgagatt ctcatacatg gctataatag aaggagcaaa atgtataaag 900
ggagattcta gtatacagaa acgatggaaa gaactttcta aggaagactt atctcctgcc 960
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gaagaagaaa aactgacagg tgaccgatgt acaggacttt cctctaaaat gcaagataca 1080
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acagctcaga aggtgcagca gatgaaacag aggctaaatg agaatgaacg aaaaagaaaa 1200
aggtggttat attggcaacc tattctcact aagatggggt ttatgtcagt cattttggtt 1260
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gcccagcaag cttctgcact agtaactgac agtgctacat taatcatagg ggtttgtctg 1380
cagcaaacgc ctcatatccc aaaaacggtg cagtagaata gacatcaacc agataagtga 1440
tatttacagt cacaagccca acatctcagg actcttgact gcaggttcct ctgaacccca 1500
aactgtaaat ggctgtctaa aataaagaca ttcatgtttg ttaaaaactg gtaaattttg 1560
caactgtatt catacatgtc aaacacagta tttcacctga ccaacattga gatatccttt 1620
atcacaggat ttgtttttgg aggctatctg gattttaacc tgcacttgat ataagcaata 1680
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atattttata agtatctatt taatcttttg tagttaactg tacttttttaa gagctcaatt 1860
tgaaaaatct gttactaaaa aaaaaaattg tatgtcgatt gaattgtact ggatacattt 1920
tccatttttc taaaaagaag tttgatatga gcagttagaa gttggaataa gcaatttcta 1980
ctatatattg catttctttt atgttttaca gttttcccca ttttaaaaag aaaagcaaac 2040
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tcaggtaaac agttggtcaa gactttgtaa agaaattggt ttctgtaaat cccattattg 2160
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taaaccc 2287

<210> 164
<211> 415
<212> PRT
<213> Homo sapiens

<400> 164

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Arg	Trp	Gln	Pro	Leu	Tyr	Leu	Glu	Ile	Arg	Asn	Glu	Ser	His	Asp	Tyr
			20					25					30		
Pro	His	Arg	Val	Ala	Lys	Phe	Pro	Glu	Asn	Arg	Asn	Arg	Asn	Arg	Tyr
		35					40					45			
Arg	Asp	Val	Ser	Pro	Tyr	Asp	His	Ser	Arg	Val	Lys	Leu	Gln	Asn	Ala
	50					55					60				
Glu	Asn	Asp	Tyr	Ile	Asn	Ala	Ser	Leu	Val	Asp	Ile	Glu	Glu	Ala	Gln
65					70					75					80
Arg	Ser	Tyr	Ile	Leu	Thr	Gln	Gly	Pro	Leu	Pro	Asn	Thr	Cys	Cys	His
				85					90					95	
Phe	Trp	Leu	Met	Val	Trp	Gln	Gln	Lys	Thr	Lys	Ala	Val	Val	Met	Leu
			100					105					110		
Asn	Arg	Ile	Val	Glu	Lys	Glu	Ser	Val	Lys	Cys	Ala	Gln	Tyr	Trp	Pro
		115					120					125			
Thr	Asp	Asp	Gln	Glu	Met	Leu	Phe	Lys	Glu	Thr	Gly	Phe	Ser	Val	Lys
	130					135					140				
Leu	Leu	Ser	Glu	Asp	Val	Lys	Ser	Tyr	Tyr	Thr	Val	His	Leu	Leu	Gln
145					150					155					160
Leu	Glu	Asn	Ile	Asn	Ser	Gly	Glu	Thr	Arg	Thr	Ile	Ser	His	Phe	His
				165					170					175	
Tyr	Thr	Thr	Trp	Pro	Asp	Phe	Gly	Val	Pro	Glu	Ser	Pro	Ala	Ser	Phe
			180					185					190		
Leu	Asn	Phe	Leu	Phe	Lys	Val	Arg	Glu	Ser	Gly	Ser	Leu	Asn	Pro	Asp
		195					200					205			
His	Gly	Pro	Ala	Val	Ile	His	Cys	Ser	Ala	Gly	Ile	Gly	Arg	Ser	Gly
	210					215					220				
Thr	Phe	Ser	Leu	Val	Asp	Thr	Cys	Leu	Val	Leu	Met	Glu	Lys	Gly	Asp
225					230					235					240
Asp	Ile	Asn	Ile	Lys	Gln	Val	Leu	Leu	Asn	Met	Arg	Lys	Tyr	Arg	Met
				245					250					255	
Gly	Leu	Ile	Gln	Thr	Pro	Asp	Gln	Leu	Arg	Phe	Ser	Tyr	Met	Ala	Ile
			260					265					270		
Ile	Glu	Gly	Ala	Lys	Cys	Ile	Lys	Gly	Asp	Ser	Ser	Ile	Gln	Lys	Arg
		275					280					285			
Trp	Lys	Glu	Leu	Ser	Lys	Glu	Asp	Leu	Ser	Pro	Ala	Phe	Asp	His	Ser
	290					295					300				
Pro	Asn	Lys	Ile	Met	Thr	Glu	Lys	Tyr	Asn	Gly	Asn	Arg	Ile	Gly	Leu
305					310					315					320

Glu Glu Glu Lys Leu Thr Gly Asp Arg Cys Thr Gly Leu Ser Ser Lys
325 330 335
Met Gln Asp Thr Met Glu Glu Asn Ser Glu Ser Ala Leu Arg Lys Arg
340 345 350
Ile Arg Glu Asp Arg Lys Ala Thr Thr Ala Gln Lys Val Gln Gln Met
355 360 365
Lys Gln Arg Leu Asn Glu Asn Glu Arg Lys Arg Lys Arg Trp Leu Tyr
370 375 380
Trp Gln Pro Ile Leu Thr Lys Met Gly Phe Met Ser Val Ile Leu Val
385 390 395 400
Gly Ala Phe Val Gly Trp Arg Leu Phe Phe Gln Gln Asn Ala Leu
405 410 415

<210> 165
<211> 2477
<212> DNA
<213> Homo sapiens

<400> 165
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tctccccgga tcgtgcgggg cctgagcctc tccgccggcg caggctctgc tcgcgccagc 180
tcgctcccgc agccatgccc accaccatcg agcgggagtt cgaagagttg gatactcagc 240
gtcgctggca gccgctgtac ttggaaattc gaaatgagtc ccatgactat cctcatagag 300
tggccaagtt tccagaaaac agaaatcgaa acagatacag agatgtaagc ccatatgatc 360
acagtcgtgt taaactgcaa aatgctgaga atgattatat taatgccagt ttagttgaca 420
tagaagaggc acaaaggagt tacatcttaa cacagggtcc acttcctaac acatgctgcc 480
atttctggct tatggtttgg cagcagaaga ccaaagcagt tgtcatgctg aaccgcattg 540
tggagaaaga atcggttaaa tgtgcacagt actggccaac agatgaccaa gagatgctgt 600
ttaaagaaac aggattcagt gtgaagctct tgtcagaaga tgtgaagtcg tattatacag 660
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attatactac ctggccagat tttggagtcc ctgaatcacc agcttcattt ctcaatttct 780
tgtttaaagt gagagaatct ggctccttga accctgacca tgggcctgcg gtgatccact 840
gtagtgcagg cattgggcgc tctggcacct tctctctggt agacacttgt cttgttttga 900
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<210> 166
<211> 415
<212> PRT
<213> Homo sapiens

<400> 166

Met	Pro	Thr	Thr	Ile	Glu	Arg	Glu	Phe	Glu	Glu	Leu	Asp	Thr	Gln	Arg
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Arg	Trp	Gln	Pro	Leu	Tyr	Leu	Glu	Ile	Arg	Asn	Glu	Ser	His	Asp	Tyr
			20					25					30		
Pro	His	Arg	Val	Ala	Lys	Phe	Pro	Glu	Asn	Arg	Asn	Arg	Asn	Arg	Tyr
		35					40					45			
Arg	Asp	Val	Ser	Pro	Tyr	Asp	His	Ser	Arg	Val	Lys	Leu	Gln	Asn	Ala
	50					55					60				
Glu	Asn	Asp	Tyr	Ile	Asn	Ala	Ser	Leu	Val	Asp	Ile	Glu	Glu	Ala	Gln
65					70					75					80
Arg	Ser	Tyr	Ile	Leu	Thr	Gln	Gly	Pro	Leu	Pro	Asn	Thr	Cys	Cys	His
				85					90					95	
Phe	Trp	Leu	Met	Val	Trp	Gln	Gln	Lys	Thr	Lys	Ala	Val	Val	Met	Leu
			100					105					110		
Asn	Arg	Ile	Val	Glu	Lys	Glu	Ser	Val	Lys	Cys	Ala	Gln	Tyr	Trp	Pro
		115					120					125			
Thr	Asp	Asp	Gln	Glu	Met	Leu	Phe	Lys	Glu	Thr	Gly	Phe	Ser	Val	Lys
	130					135					140				
Leu	Leu	Ser	Glu	Asp	Val	Lys	Ser	Tyr	Tyr	Thr	Val	His	Leu	Leu	Gln
145					150					155					160
Leu	Glu	Asn	Ile	Asn	Ser	Gly	Glu	Thr	Arg	Thr	Ile	Ser	His	Phe	His
				165					170					175	
Tyr	Thr	Thr	Trp	Pro	Asp	Phe	Gly	Val	Pro	Glu	Ser	Pro	Ala	Ser	Phe
			180					185					190		
Leu	Asn	Phe	Leu	Phe	Lys	Val	Arg	Glu	Ser	Gly	Ser	Leu	Asn	Pro	Asp
		195					200					205			
His	Gly	Pro	Ala	Val	Ile	His	Cys	Ser	Ala	Gly	Ile	Gly	Arg	Ser	Gly
	210					215					220				
Thr	Phe	Ser	Leu	Val	Asp	Thr	Cys	Leu	Val	Leu	Met	Glu	Lys	Gly	Asp
225					230					235					240
Asp	Ile	Asn	Ile	Lys	Gln	Val	Leu	Leu	Asn	Met	Arg	Lys	Tyr	Arg	Met
				245					250					255	
Gly	Leu	Ile	Gln	Thr	Pro	Asp	Gln	Leu	Arg	Phe	Ser	Tyr	Met	Ala	Ile
			260					265					270		
Ile	Glu	Gly	Ala	Lys	Cys	Ile	Lys	Gly	Asp	Ser	Ser	Ile	Gln	Lys	Arg
		275					280					285			
Trp	Lys	Glu	Leu	Ser	Lys	Glu	Asp	Leu	Ser	Pro	Ala	Phe	Asp	His	Ser
	290					295					300				
Pro	Asn	Lys	Ile	Met	Thr	Glu	Lys	Tyr	Asn	Gly	Asn	Arg	Ile	Gly	Leu
305					310					315					320
Glu	Glu	Glu	Lys	Leu	Thr	Gly	Asp	Arg	Cys	Thr	Gly	Leu	Ser	Ser	Lys
				325					330					335	
Met	Gln	Asp	Thr	Met	Glu	Glu	Asn	Ser	Glu	Ser	Ala	Leu	Arg	Lys	Arg
			340					345					350		
Ile	Arg	Glu	Asp	Arg	Lys	Ala	Thr	Thr	Ala	Gln	Lys	Val	Gln	Gln	Met
		355					360					365			
Lys	Gln	Arg	Leu	Asn	Glu	Asn	Glu	Arg	Lys	Arg	Lys	Arg	Trp	Leu	Tyr

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    370                 375                 380
Trp Gln Pro Ile Leu Thr Lys Met Gly Phe Met Ser Val Ile Leu Val
385                 390                 395                 400
Gly Ala Phe Val Gly Trp Arg Leu Phe Phe Gln Gln Asn Ala Leu
                405                 410                 415
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<210> 167
<211> 1714
<212> DNA
<213> Homo sapiens

<400> 167

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tagaagaggc acaaaggagt tacatcttaa cacagggtcc acttcctaac acatgctgcc 480
atttctggct tatggtttgg cagcagaaga ccaaagcagt tgtcatgctg aaccgcattg 540
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gtagtgcagg cattgggcgc tctggcacct tctctctggt agacacttgt cttgttttga 900
tggaaaaagg agatgatatt aacataaaac aagtgttact gaacatgaga aaataccgaa 960
tgggtcttat tcagacccca gatcaactga gattctcata catggctata atagaaggag 1020
caaaatgtat aaagggagat tctagtatac agaaacgatg gaaagaactt tctaaggaag 1080
acttatctcc tgcctttgat cattcaccaa acaaaataat gactgaaaaa tacaatggga 1140
acagaatagg tctagaagaa gaaaaactga caggtgaccg atgtacagga ctttcctcta 1200
aaatgcaaga tacaatggag gagaacagtg agagtgctct acggaaacgt attcgagagg 1260
acagaaaggc caccacagct cagaaggtgc agcagatgaa acagaggcta aatgagaatg 1320
aacgaaaaag aaaaaggcca agattgacag acacctaata ttcatgactt gagaatattc 1380
tgcagctata aattttgaac cattgatgtg caaagcaaga cctgaagccc actccggaaa 1440
ctaaagtgag gctcgctaac cctctagatt gcctcacagt tgtttgttta caaagtaaac 1500
tttacatcca ggggatgaag agcacccacc agcagaagac tttgcagaac ctttaattgg 1560
atgtgttaag tgtttttaat gagtgtatga aatgtagaaa gatgtacaag aaataaatta 1620
ggagagatta ctttgtattg tactgccatt cctactgtat ttttatactt tttggcagca 1680
ttaaatattt ttgttaaata aaaaaaaaaa aaaa                              1714
```

<210> 168
<211> 387
<212> PRT
<213> Homo sapiens

<400> 168

```
Met Pro Thr Thr Ile Glu Arg Glu Phe Glu Glu Leu Asp Thr Gln Arg
 1               5                  10                  15
Arg Trp Gln Pro Leu Tyr Leu Glu Ile Arg Asn Glu Ser His Asp Tyr
            20                  25                  30
Pro His Arg Val Ala Lys Phe Pro Glu Asn Arg Asn Arg Asn Arg Tyr
        35                  40                  45
Arg Asp Val Ser Pro Tyr Asp His Ser Arg Val Lys Leu Gln Asn Ala
    50                  55                  60
Glu Asn Asp Tyr Ile Asn Ala Ser Leu Val Asp Ile Glu Glu Ala Gln
```

65 70 75 80
Arg Ser Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Cys His
85 90 95
Phe Trp Leu Met Val Trp Gln Gln Lys Thr Lys Ala Val Val Met Leu
100 105 110
Asn Arg Ile Val Glu Lys Glu Ser Val Lys Cys Ala Gln Tyr Trp Pro
115 120 125
Thr Asp Asp Gln Glu Met Leu Phe Lys Glu Thr Gly Phe Ser Val Lys
130 135 140
Leu Leu Ser Glu Asp Val Lys Ser Tyr Tyr Thr Val His Leu Leu Gln
145 150 155 160
Leu Glu Asn Ile Asn Ser Gly Glu Thr Arg Thr Ile Ser His Phe His
165 170 175
Tyr Thr Thr Trp Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe
180 185 190
Leu Asn Phe Leu Phe Lys Val Arg Glu Ser Gly Ser Leu Asn Pro Asp
195 200 205
His Gly Pro Ala Val Ile His Cys Ser Ala Gly Ile Gly Arg Ser Gly
210 215 220
Thr Phe Ser Leu Val Asp Thr Cys Leu Val Leu Met Glu Lys Gly Asp
225 230 235 240
Asp Ile Asn Ile Lys Gln Val Leu Leu Asn Met Arg Lys Tyr Arg Met
245 250 255
Gly Leu Ile Gln Thr Pro Asp Gln Leu Arg Phe Ser Tyr Met Ala Ile
260 265 270
Ile Glu Gly Ala Lys Cys Ile Lys Gly Asp Ser Ser Ile Gln Lys Arg
275 280 285
Trp Lys Glu Leu Ser Lys Glu Asp Leu Ser Pro Ala Phe Asp His Ser
290 295 300
Pro Asn Lys Ile Met Thr Glu Lys Tyr Asn Gly Asn Arg Ile Gly Leu
305 310 315 320
Glu Glu Glu Lys Leu Thr Gly Asp Arg Cys Thr Gly Leu Ser Ser Lys
325 330 335
Met Gln Asp Thr Met Glu Glu Asn Ser Glu Ser Ala Leu Arg Lys Arg
340 345 350
Ile Arg Glu Asp Arg Lys Ala Thr Thr Ala Gln Lys Val Gln Gln Met
355 360 365
Lys Gln Arg Leu Asn Glu Asn Glu Arg Lys Arg Lys Arg Pro Arg Leu
370 375 380
Thr Asp Thr
385

<210> 169
<211> 79
<212> PRT
<213> Unknown

<220>
<223> Catalytic domain region

<400> 169
Phe Asn Asn Glu Thr Arg Ile Ile Tyr Gln Phe His Tyr Lys Asn Trp
1 5 10 15
Pro Asp His Asp Val Pro Ser Ser Ile Asp Pro Ile Leu Gln Leu Ile
20 25 30
Trp Asp Met Arg Cys Tyr Gln Glu Asp Asp Cys Val Pro Ile Cys Ile
35 40 45

His Cys Ser Ala Gly Cys Gly Arg Thr Gly Val Ile Cys Ala Val Asp
50 55 60
Tyr Thr Trp Met Leu Leu Lys Asp Gly Ile Ile Pro Lys Asn Phe
65 70 75

<210> 170
<211> 79
<212> PRT
<213> Unknown

<220>
<223> Catalytic domain region

<400> 170
Phe Gln Asn Glu Ser Arg Arg Leu Tyr Gln Phe His Tyr Val Asn Trp
1 5 10 15
Pro Asp His Asp Val Pro Ser Ser Phe Asp Ser Ile Leu Asp Met Ile
20 25 30
Ser Leu Met Arg Lys Tyr Gln Glu His Glu Asp Val Pro Ile Cys Ile
35 40 45
His Cys Ser Ala Gly Cys Gly Arg Thr Gly Ala Ile Cys Ala Ile Asp
50 55 60
Tyr Thr Trp Asn Leu Leu Lys Ala Gly Lys Ile Pro Glu Glu Phe
65 70 75

<210> 171
<211> 79
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 171
Phe Gln Lys Glu Ser Arg Ser Val Tyr Gln Leu Gln Tyr Met Ser Trp
1 5 10 15
Pro Asp Arg Gly Val Pro Ser Ser Pro Asp His Met Leu Ala Met Val
20 25 30
Glu Glu Ala Arg Arg Leu Gln Gly Ser Gly Pro Glu Pro Leu Cys Val
35 40 45
His Cys Ser Ala Gly Cys Gly Arg Thr Gly Val Leu Cys Thr Val Asp
50 55 60
Tyr Val Arg Gln Leu Leu Leu Thr Gln Met Ile Pro Pro Asp Phe
65 70 75

<210> 172
<211> 82
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 172
Asp Asn Gly Asp Leu Ile Arg Glu Ile Trp His Tyr Gln Tyr Leu Ser

```
 1               5                  10                  15
Trp Pro Asp His Gly Val Pro Ser Glu Pro Gly Gly Val Leu Ser Phe
            20                  25                  30
Leu Asp Gln Ile Asn Gln Arg Gln Glu Ser Leu Pro His Ala Gly Pro
        35                  40                  45
Ile Ile Val His Cys Ser Ala Gly Ile Gly Arg Thr Gly Thr Ile Ile
    50                  55                  60
Val Ile Asp Met Leu Met Glu Asn Ile Ser Thr Lys Gly Leu Asp Cys
65                  70                  75                  80
Asp Ile
```

<210> 173
<211> 82
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 173

```
Gly Gln Gly Asn Thr Glu Arg Thr Val Trp Gln Tyr His Phe Arg Thr
 1               5                  10                  15
Trp Pro Asp His Gly Val Pro Ser Asp Pro Gly Gly Val Leu Asp Phe
            20                  25                  30
Leu Glu Glu Val His His Lys Gln Glu Ser Ile Met Asp Ala Gly Pro
        35                  40                  45
Val Val Val His Cys Ser Ala Gly Ile Gly Arg Thr Gly Thr Phe Ile
    50                  55                  60
Val Ile Asp Ile Leu Ile Asp Ile Ile Arg Glu Lys Gly Val Asp Cys
65                  70                  75                  80
Asp Ile
```

<210> 174
<211> 75
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 174

```
Val His Glu Ile Arg Glu Ile Arg Gln Phe His Phe Thr Gly Trp Pro
 1               5                  10                  15
Asp His Gly Val Pro Tyr His Ala Thr Gly Leu Leu Gly Phe Val Arg
            20                  25                  30
Gln Val Lys Ser Lys Ser Pro Pro Ser Ala Gly Pro Leu Val Val His
        35                  40                  45
Cys Ser Ala Gly Ala Gly Arg Thr Gly Cys Phe Ile Val Ile Asp Ile
    50                  55                  60
Met Leu Asp Met Ala Glu Arg Glu Gly Val Val
65                  70                  75
```

<210> 175

<211> 75
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 175
Tyr Asn Glu Ile Arg Glu Val Lys Gln Phe His Phe Thr Gly Trp Pro
1 5 10 15
Asp His Gly Val Pro Tyr His Ala Thr Gly Leu Leu Ser Phe Ile Arg
20 25 30
Arg Val Lys Leu Ser Asn Pro Pro Ser Ala Gly Pro Ile Val Val His
35 40 45
Cys Ser Ala Gly Ala Gly Arg Thr Gly Cys Tyr Ile Val Ile Asp Ile
50 55 60
Met Leu Asp Met Ala Glu Arg Glu Gly Val Val
65 70 75

<210> 176
<211> 75
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 176
Tyr His Glu Ile Arg Glu Leu Arg Leu Phe His Phe Thr Ser Trp Pro
1 5 10 15
Asp His Gly Val Pro Cys Tyr Ala Thr Gly Leu Leu Gly Phe Val Arg
20 25 30
Gln Val Lys Phe Leu Asn Pro Pro Glu Ala Gly Pro Ile Val Val His
35 40 45
Cys Ser Ala Gly Ala Gly Arg Thr Gly Cys Phe Ile Ala Ile Asp Thr
50 55 60
Met Leu Asp Met Ala Glu Asn Glu Gly Val Val
65 70 75

<210> 177
<211> 75
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 177
Ser Ser Glu Lys Arg Glu Val Arg Gln Phe Gln Phe Thr Ala Trp Pro
1 5 10 15
Asp His Gly Val Pro Glu His Pro Thr Pro Phe Leu Ala Phe Leu Arg
20 25 30
Arg Val Lys Thr Cys Asn Pro Pro Asp Ala Gly Pro Met Val Val His
35 40 45
Cys Ser Ala Gly Val Gly Arg Thr Gly Cys Phe Ile Val Ile Asp Ala
50 55 60

Met Leu Glu Arg Ile Lys His Glu Lys Thr Val
65 70 75

<210> 178
<211> 75
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 178
Ser Ser Glu Lys Arg Glu Val Arg Gln Phe Gln Phe Thr Ala Trp Pro
1 5 10 15
Asp His Gly Val Pro Glu Tyr Pro Thr Pro Phe Leu Ala Phe Leu Arg
20 25 30
Arg Val Lys Thr Cys Asn Pro Pro Asp Ala Gly Pro Ile Val Val His
35 40 45
Cys Ser Ala Gly Val Gly Arg Thr Gly Cys Phe Ile Val Ile Asp Ala
50 55 60
Met Leu Glu Arg Ile Lys Pro Glu Lys Thr Val
65 70 75

<210> 179
<211> 75
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 179
Ser Ser Glu Lys Arg Glu Leu Arg Gln Phe Gln Phe Met Ala Trp Pro
1 5 10 15
Asp His Gly Val Pro Glu Tyr Pro Thr Pro Ile Leu Ala Phe Leu Arg
20 25 30
Arg Val Lys Ala Cys Asn Pro Leu Asp Ala Gly Pro Met Val Val His
35 40 45
Cys Ser Ala Gly Val Gly Arg Thr Gly Cys Phe Ile Val Ile Asp Ala
50 55 60
Met Leu Glu Arg Met Lys His Glu Lys Thr Val
65 70 75

<210> 180
<211> 79
<212> PRT
<213> Unknown

<220>
<223> Catalytic domain region

<400> 180
Asp Met Thr Asn Arg Lys Pro Gln Arg Leu Ile Thr Gln Phe His Phe
1 5 10 15
Thr Ser Trp Pro Asp Phe Gly Val Pro Phe Thr Pro Ile Gly Met Leu

```
            20                  25                  30
Lys Phe Leu Lys Lys Val Lys Ala Cys Asn Pro Gln Tyr Ala Gly Ala
        35                  40                  45
Ile Val Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Phe Val
    50                  55                  60
Val Ile Asp Ala Met Leu Asp Met Met His Thr Glu Arg Lys Val
65                  70                  75
```

<210> 181
<211> 78
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 181

```
Pro Asp Gly Cys Lys Ala Pro Arg Leu Val Ser Gln Leu His Phe Thr
 1               5                  10                  15
Ser Trp Pro Asp Phe Gly Val Pro Phe Thr Pro Ile Gly Met Leu Lys
            20                  25                  30
Phe Leu Lys Lys Val Lys Thr Leu Asn Pro Val His Ala Gly Pro Ile
        35                  40                  45
Val Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Phe Ile Val
    50                  55                  60
Ile Asp Ala Met Met Ala Met Met His Ala Glu Gln Lys Val
65                  70                  75
```

<210> 182
<211> 82
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 182

```
Gln Lys Gly Asn Pro Lys Gly Arg Gln Asn Glu Arg Val Val Ile Gln
 1               5                  10                  15
Tyr His Tyr Thr Gln Trp Pro Asp Met Gly Val Pro Glu Tyr Ala Leu
            20                  25                  30
Pro Val Leu Thr Phe Val Arg Arg Ser Ser Ala Ala Arg Met Pro Glu
        35                  40                  45
Thr Gly Pro Val Leu Val His Cys Ser Ala Gly Val Gly Arg Thr Gly
    50                  55                  60
Thr Tyr Ile Val Ile Asp Ser Met Leu Gln Gln Ile Lys Asp Lys Ser
65                  70                  75                  80
Thr Val
```

<210> 183
<211> 79
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 183
Ser Gln Lys Gly Arg Pro Ser Gly Arg Val Val Thr Gln Tyr His Tyr
1 5 10 15
Thr Gln Trp Pro Asp Met Gly Val Pro Glu Tyr Ser Leu Pro Val Leu
20 25 30
Thr Phe Val Arg Lys Ala Ala Tyr Ala Lys Arg His Ala Val Gly Pro
35 40 45
Val Val Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Tyr Ile
50 55 60
Val Leu Asp Ser Met Leu Gln Gln Ile Gln His Glu Gly Thr Val
65 70 75

<210> 184
<211> 77
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 184
Lys Glu Lys Ala Thr Gly Arg Glu Val Thr His Ile Gln Phe Thr Ser
1 5 10 15
Trp Pro Asp His Gly Val Pro Glu Asp Pro His Leu Leu Leu Lys Leu
20 25 30
Arg Arg Arg Val Asn Ala Phe Ser Asn Phe Phe Ser Gly Pro Ile Val
35 40 45
Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Tyr Ile Gly Ile
50 55 60
Asp Ala Met Leu Glu Gly Leu Glu Ala Glu Asn Lys Val
65 70 75

<210> 185
<211> 79
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 185
Glu Gln Leu Asp Ala His Arg Leu Ile Arg His Phe His Tyr Thr Val
1 5 10 15
Trp Pro Asp His Gly Val Pro Glu Thr Thr Gln Ser Leu Ile Gln Phe
20 25 30
Val Arg Thr Val Arg Asp Tyr Ile Asn Arg Ser Pro Gly Ala Gly Pro
35 40 45
Thr Val Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Phe Ile
50 55 60
Ala Leu Asp Arg Ile Leu Gln Gln Leu Asp Ser Lys Asp Ser Val
65 70 75

<210> 186
<211> 78
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 186
Gln Thr Ser Glu Ser His Pro Leu Arg Gln Phe His Phe Thr Ser Trp
1 5 10 15
Pro Asp His Gly Val Pro Asp Thr Thr Asp Leu Leu Ile Asn Phe Arg
20 25 30
Tyr Leu Val Arg Asp Tyr Met Lys Gln Ser Pro Pro Glu Ser Pro Ile
35 40 45
Leu Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Phe Ile Ala
50 55 60
Ile Asp Arg Leu Ile Tyr Gln Ile Glu Asn Glu Asn Thr Val
65 70 75

<210> 187
<211> 76
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 187
Asp Glu Met Gln Asp Val Met His Phe Asn Tyr Thr Ala Trp Pro Asp
1 5 10 15
His Gly Val Pro Thr Ala Asn Ala Ala Glu Ser Ile Leu Gln Phe Val
20 25 30
His Met Val Arg Gln Gln Ala Thr Lys Ser Lys Gly Pro Met Ile Ile
35 40 45
His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Phe Ile Ala Leu Asp
50 55 60
Arg Leu Leu Gln His Ile Arg Asp His Glu Phe Val
65 70 75

<210> 188
<211> 72
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 188
Gly Asp Cys Met Thr Val Arg Gln Phe Thr Gly Trp Pro Glu His Gly
1 5 10 15
Val Pro Glu Asn Thr Thr Pro Leu Ile His Phe Val Lys Leu Val Arg
20 25 30
Thr Ser Arg Ala His Asp Thr Thr Pro Met Val Val His Cys Ser Ala
35 40 45
Gly Val Gly Arg Thr Gly Val Phe Ile Ala Leu Asp His Leu Thr Gln

50 55 60
His Ile Asn Asn His Asp Phe Val
65 70

<210> 189
<211> 78
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 189
Arg Asp Gly Gln Ser Arg Thr Val Arg Gln Phe Gln Phe Thr Asp Trp
1 5 10 15
Pro Glu Gln Gly Val Pro Lys Ser Gly Glu Gly Phe Ile Asp Phe Ile
20 25 30
Gly Gln Val His Lys Thr Lys Glu Gln Phe Gly Gln Asp Gly Pro Ile
35 40 45
Ser Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Val Phe Ile Thr
50 55 60
Leu Ser Ile Val Leu Glu Arg Met Arg Tyr Glu Gly Val Val
65 70 75

<210> 190
<211> 78
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 190
Arg Asp Gly Gln Ser Arg Thr Val Arg Gln Phe Gln Phe Thr Asp Trp
1 5 10 15
Pro Glu Gln Gly Val Pro Lys Ser Gly Glu Gly Phe Ile Asp Phe Ile
20 25 30
Gly Gln Val His Lys Thr Lys Glu Gln Phe Gly Gln Asp Gly Pro Ile
35 40 45
Ser Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Val Phe Ile Thr
50 55 60
Leu Ser Ile Val Leu Glu Arg Met Arg Tyr Glu Gly Val Val
65 70 75

<210> 191
<211> 78
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 191
Arg Asp Gly Gln Ser Arg Thr Ile Arg Gln Phe Gln Phe Thr Asp Trp
1 5 10 15

Pro Glu Gln Gly Val Pro Lys Thr Gly Glu Gly Phe Ile Asp Phe Ile
20 25 30
Gly Gln Val His Lys Thr Lys Glu Gln Phe Gly Gln Asp Gly Pro Ile
35 40 45
Thr Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Val Phe Ile Thr
50 55 60
Leu Ser Ile Val Leu Glu Arg Met Arg Tyr Glu Gly Val Val
65 70 75

<210> 192
<211> 77
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 192
Arg Glu Asn Lys Ser Arg Gln Ile Arg Gln Phe His Phe His Gly Trp
1 5 10 15
Pro Glu Val Gly Ile Pro Ser Asp Gly Lys Gly Met Ile Ser Ile Ile
20 25 30
Ala Ala Val Gln Lys Gln Gln Gln Gln Ser Gly Asn His Pro Ile Thr
35 40 45
Val His Cys Ser Ala Gly Ala Gly Arg Thr Gly Thr Phe Cys Ala Leu
50 55 60
Ser Thr Val Leu Glu Arg Val Lys Ala Glu Gly Ile Leu
65 70 75

<210> 193
<211> 82
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 193
Gln Pro Gln Ala Arg Gln Glu Glu Gln Val Arg Val Val Arg Gln Phe
1 5 10 15
His Phe His Gly Trp Pro Glu Ile Gly Ile Pro Ala Glu Gly Lys Gly
20 25 30
Met Ile Asp Leu Ile Ala Ala Val Gln Lys Gln Gln Gln Gln Thr Gly
35 40 45
Asn His Pro Ile Thr Val His Cys Ser Ala Gly Ala Gly Arg Thr Gly
50 55 60
Thr Phe Ile Ala Leu Ser Asn Ile Leu Glu Arg Val Lys Ala Glu Gly
65 70 75 80
Leu Leu

<210> 194
<211> 78
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 194
Asn Ser Gly Glu Thr Arg Thr Ile Ser His Phe His Tyr Thr Thr Trp
1 5 10 15
Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe Leu Asn Phe Leu
20 25 30
Phe Lys Val Arg Glu Ser Gly Ser Leu Asn Pro Asp His Gly Pro Ala
35 40 45
Val Ile His Cys Ser Ala Gly Ile Gly Arg Ser Gly Thr Phe Ser Leu
50 55 60
Val Asp Thr Cys Leu Val Leu Met Glu Lys Gly Asp Asp Ile
65 70 75

<210> 195
<211> 81
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 195
Thr Thr Gln Glu Thr Arg Glu Ile Leu His Phe His Tyr Thr Thr Trp
1 5 10 15
Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe Leu Asn Phe Leu
20 25 30
Phe Lys Val Arg Glu Ser Gly Ser Leu Ser Pro Glu His Gly Pro Val
35 40 45
Val Val His Cys Ser Ala Gly Ile Gly Arg Ser Gly Thr Phe Cys Leu
50 55 60
Ala Asp Thr Cys Leu Leu Leu Met Asp Lys Arg Lys Asp Pro Ser Ser
65 70 75 80
Val

<210> 196
<211> 89
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 196
Glu Glu Arg Gln Lys Arg Gln Val Thr His Phe Gln Phe Leu Ser Trp
1 5 10 15
Pro Asp Tyr Gly Val Pro Ser Ser Ala Ala Ser Leu Ile Asp Phe Leu
20 25 30
Arg Val Val Arg Asn Gln Gln Ser Leu Ala Val Ser Asn Met Gly Ala
35 40 45
Arg Ser Lys Gly Gln Cys Pro Glu Pro Pro Ile Val Val His Cys Ser
50 55 60
Ala Gly Ile Gly Arg Thr Gly Thr Phe Cys Ser Leu Asp Ile Cys Leu

65 70 75 80
Ala Gln Leu Glu Glu Leu Gly Thr Leu
85

<210> 197
<211> 77
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 197
Gln Thr Gln Glu Thr Arg Thr Leu Thr Gln Phe His Phe Leu Ser Trp
1 5 10 15
Pro Ala Glu Gly Thr Pro Ala Ser Thr Arg Pro Leu Leu Asp Phe Arg
20 25 30
Arg Lys Val Asn Lys Cys Tyr Arg Gly Arg Ser Cys Pro Ile Ile Val
35 40 45
His Cys Ser Asp Gly Ala Gly Arg Thr Gly Thr Tyr Ile Leu Ile Asp
50 55 60
Met Val Leu Asn Arg Met Ala Lys Gly Val Lys Glu Ile
65 70 75

<210> 198
<211> 77
<212> PRT
<213> Unknown

<220>
<223> Catalytic domain region

<400> 198
Gln Thr Asn Glu Thr Arg Thr Val Thr Gln Phe His Phe Leu Ser Trp
1 5 10 15
Tyr Asp Arg Gly Val Pro Ser Ser Ser Arg Ser Leu Leu Asp Phe Arg
20 25 30
Arg Lys Val Asn Lys Cys Tyr Arg Gly Arg Ser Cys Pro Ile Ile Val
35 40 45
His Cys Ser Asp Gly Ala Gly Arg Ser Gly Thr Tyr Val Leu Ile Asp
50 55 60
Met Val Leu Asn Lys Met Ala Lys Gly Ala Lys Glu Ile
65 70 75

<210> 199
<211> 86
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 199
Lys Arg Lys Asp Ser Arg Thr Val Tyr Gln Tyr Gln Tyr Thr Asn Trp
1 5 10 15

```
Ser Val Glu Gln Leu Pro Ala Glu Pro Lys Glu Leu Ile Ser Met Ile
            20                  25                  30
Gln Val Val Lys Gln Lys Leu Pro Gln Lys Asn Ser Ser Glu Gly Asn
        35                  40                  45
Lys His His Lys Ser Thr Pro Leu Leu Ile His Cys Arg Asp Gly Ser
    50                  55                  60
Gln Gln Thr Gly Ile Phe Cys Ala Leu Leu Asn Leu Leu Glu Ser Ala
65                  70                  75                  80
Glu Thr Glu Glu Val Val
                85
```

<210> 200
<211> 78
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 200

```
Gln Gly Ser His Thr Gln His Val Lys His Tyr Trp Tyr Thr Ser Trp
 1               5                  10                  15
Pro Asp His Lys Thr Pro Asp Ser Ala Gln Pro Leu Leu Gln Leu Met
            20                  25                  30
Leu Asp Val Glu Glu Asp Arg Leu Ala Ser Gln Gly Arg Gly Pro Val
        35                  40                  45
Val Val His Cys Ser Ala Gly Ile Gly Arg Thr Gly Cys Phe Ile Ala
    50                  55                  60
Thr Ser Ile Gly Cys Gln Gln Leu Lys Glu Glu Gly Val Val
65                  70                  75
```

<210> 201
<211> 79
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 201

```
Ser Gly Thr Glu Glu Arg Gly Leu Lys His Tyr Trp Phe Thr Ser Trp
 1               5                  10                  15
Pro Asp Gln Lys Thr Pro Asp Arg Ala Pro Pro Leu Leu His Leu Val
            20                  25                  30
Arg Glu Val Glu Glu Ala Ala Gln Gln Glu Gly Pro His Cys Ala Pro
        35                  40                  45
Ile Ile Val His Cys Ser Ala Gly Ile Gly Arg Thr Gly Cys Phe Ile
    50                  55                  60
Ala Thr Ser Ile Cys Cys Gln Gln Leu Arg Gln Glu Gly Val Val
65                  70                  75
```

<210> 202
<211> 86
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 202
Leu Ser Gly Gln Glu Arg Thr Val Trp His Leu Gln Tyr Thr Asp Trp
1 5 10 15
Pro Asp His Gly Cys Pro Glu Asp Val Gln Gly Phe Leu Ser Tyr Leu
20 25 30
Glu Glu Ile Gln Ser Val Arg Arg His Thr Asn Ser Met Leu Glu Gly
35 40 45
Thr Lys Asn Arg His Pro Pro Ile Val Val His Cys Ser Ala Gly Val
50 55 60
Gly Arg Thr Gly Val Leu Ile Leu Ser Glu Leu Met Ile Tyr Cys Leu
65 70 75 80
Glu His Asn Glu Lys Val
85

<210> 203
<211> 85
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 203
Leu Thr Gly Gln Glu Arg Thr Val Trp His Leu Gln Tyr Thr Asp Trp
1 5 10 15
Pro Glu His Gly Cys Pro Glu Asp Leu Lys Gly Phe Leu Ser Tyr Leu
20 25 30
Glu Glu Ile Gln Ser Val Arg Arg His Thr Asn Ser Thr Ser Asp Pro
35 40 45
Gln Ser Pro Asn Pro Pro Leu Leu Val His Cys Ser Ala Gly Val Gly
50 55 60
Arg Thr Gly Val Val Ile Leu Ser Glu Ile Met Ile Ala Cys Leu Glu
65 70 75 80
His Asn Glu Val Leu
85

<210> 204
<211> 76
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 204
Glu Lys Asn Glu Ser Arg Pro Leu Thr Gln Ile Gln Tyr Ile Ala Trp
1 5 10 15
Pro Asp His Gly Val Pro Asp Asp Ser Ser Asp Phe Leu Asp Phe Val
20 25 30
Cys His Val Arg Asn Lys Arg Ala Gly Lys Glu Glu Pro Val Val Val
35 40 45
His Cys Ser Ala Gly Ile Gly Arg Thr Gly Val Leu Ile Thr Met Glu

```
    50                  55                  60
Thr Ala Met Cys Leu Ile Glu Cys Asn Gln Pro Val
65                  70                  75


<210> 205
<211> 75
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 205
Gln Thr Gly Glu Glu His Thr Val Thr His Leu Gln Tyr Val Ala Trp
 1               5                  10                  15
Pro Asp His Gly Ile Pro Asp Asp Ser Ser Asp Phe Leu Glu Phe Val
            20                  25                  30
Asn Tyr Val Arg Ser Leu Arg Val Asp Ser Glu Pro Val Leu Val His
        35                  40                  45
Cys Ser Ala Gly Ile Gly Arg Thr Gly Val Leu Val Thr Met Glu Thr
    50                  55                  60
Ala Met Cys Leu Thr Glu Arg Asn Leu Pro Ile
65                  70                  75


<210> 206
<211> 74
<212> PRT
<213> unknown

<220>
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<400> 206
Gln Thr Arg Glu Val Arg His Ile Ser His Leu Asn Phe Thr Ala Trp
 1               5                  10                  15
Pro Asp His Asp Thr Pro Ser Gln Pro Asp Asp Leu Leu Thr Phe Ile
            20                  25                  30
Ser Tyr Met Arg His Ile His Arg Ser Gly Pro Ile Ile Thr His Cys
        35                  40                  45
Ser Ala Gly Ile Gly Arg Ser Gly Thr Leu Ile Cys Ile Asp Val Val
    50                  55                  60
Leu Gly Leu Ile Ser Gln Asp Leu Asp Phe
65                  70


<210> 207
<211> 24
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 207
Gly Gly Arg Val Phe Val His Cys Gln Ala Gly Ile Ser Arg Ser Ala
 1               5                  10                  15
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Thr Ile Cys Leu Ala Tyr Leu Met
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<210> 208
<211> 24
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 208
Arg Gly Arg Val Leu Val His Cys Gln Ala Gly Ile Ser Arg Ser Ala
1 5 10 15
Thr Ile Cys Leu Ala Tyr Leu Met
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<210> 209
<211> 24
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 209
Asn Cys Gly Val Leu Val His Cys Leu Ala Gly Ile Ser Arg Ser Val
1 5 10 15
Thr Val Thr Val Ala Tyr Leu Met
20

<210> 210
<211> 24
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 210
Asn Cys Gly Val Leu Val His Cys Leu Ala Gly Val Ser Arg Ser Val
1 5 10 15
Thr Val Thr Val Ala Tyr Leu Met
20

<210> 211
<211> 24
<212> PRT
<213> unknown

<220>
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<400> 211

Gly Gly Lys Val Leu Val His Cys Glu Ala Gly Ile Ser Arg Ser Pro
1 5 10 15
Thr Ile Cys Met Ala Tyr Leu Met
20

<210> 212
<211> 24
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 212
Asn Gly Cys Val Leu Val His Cys Leu Ala Gly Ile Ser Arg Ser Ala
1 5 10 15
Thr Ile Ala Ile Ala Tyr Ile Met
20

<210> 213
<211> 24
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 213
Lys Cys Gly Val Leu Val His Cys Leu Ala Gly Ile Ser Arg Ser Val
1 5 10 15
Thr Val Thr Val Ala Tyr Leu Met
20

<210> 214
<211> 24
<212> PRT
<213> unknown

<220>
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<400> 214
Gly Gly Arg Val Leu Val His Cys Gln Ala Gly Ile Ser Arg Ser Ala
1 5 10 15
Thr Ile Cys Leu Ala Tyr Leu Ile
20

<210> 215
<211> 24
<212> PRT
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<220>
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<400> 215
Ser Cys Gln Val Ile Val His Cys Leu Ala Gly Ile Ser Arg Ser Ala
1 5 10 15
Thr Ile Ala Ile Ala Tyr Ile Met
20

<210> 216
<211> 24
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 216
Gly His Ile Val Tyr Val His Cys Asn Ala Gly Val Gly Arg Ser Thr
1 5 10 15
Ala Ala Val Cys Gly Trp Leu Gln
20

<210> 217
<211> 24
<212> PRT
<213> unknown

<220>
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<400> 217
Asn Gly Arg Val Leu Val His Cys Arg Glu Gly Tyr Ser Arg Ser Pro
1 5 10 15
Thr Leu Val Ile Ala Tyr Leu Met
20

<210> 218
<211> 24
<212> PRT
<213> unknown

<220>
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<400> 218
Gly Glu Lys Val Leu Val His Gly Asn Ala Gly Ile Ser Arg Ser Ala
1 5 10 15
Ala Phe Val Ile Ala Tyr Ile Met
20

<210> 219
<211> 24
<212> PRT
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<220>
<223> Catalytic domain region

<400> 219
Gly Ser Val Ile Leu Ile Phe Ser Thr Gln Gly Ile Ser Arg Ser Cys
1 5 10 15
Ala Ala Ile Ile Ala Tyr Leu Met
20

<210> 220
<211> 24
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 220
Ser Gly Lys Val Leu Val Ser Ser Glu Met Gly Ile Ser Arg Ser Ala
1 5 10 15
Val Leu Val Val Ala Tyr Leu Met
20

<210> 221
<211> 24
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 221
Gly Gly Ala Cys Leu Val Tyr Cys Lys Asn Gly Arg Ser Arg Ser Ala
1 5 10 15
Ala Val Cys Thr Ala Tyr Leu Met
20

<210> 222
<211> 24
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 222
Asn Gly Arg Val Leu Val His Cys Gln Ala Gly Ile Ser Arg Ser Gly
1 5 10 15
Thr Asn Ile Leu Ala Tyr Leu Met
20

<210> 223
<211> 24
<212> PRT

<213> unknown

<220>
<223> Catalytic domain region

<400> 223
Asn His Val Ala Ala Ile His Cys Lys Ala Gly Lys Gly Arg Thr Gly
1 5 10 15
Val Met Ile Cys Ala Tyr Leu Leu
20

<210> 224
<211> 24
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 224
Glu Asn Ile Val Ala Ile His Cys Lys Gly Gly Thr Asp Arg Thr Gly
1 5 10 15
Thr Met Val Cys Ala Phe Leu Ile
20

<210> 225
<211> 24
<212> PRT
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<220>
<223> Catalytic domain region

<400> 225
Glu Asn Ile Val Ala Ile His Cys Lys Gly Gly Lys Gly Arg Thr Gly
1 5 10 15
Thr Met Val Cys Ala Leu Leu Ile
20

<210> 226
<211> 24
<212> PRT
<213> unknown

<220>
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<400> 226
Glu Asn Ile Val Val Ile His Cys Lys Gly Gly Lys Gly Arg Thr Gly
1 5 10 15
Thr Met Val Cys Ala Cys Leu Ile
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<210> 227

<211> 24
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 227
Glu Asn Ile Val Val Ile His Cys Lys Gly Gly Lys Gly Arg Thr Gly
1 5 10 15
Thr Met Val Cys Ala Cys Leu Ile
20

<210> 228
<211> 24
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 228
Tyr Arg Lys Thr Leu Ile His Cys Tyr Gly Gly Leu Gly Arg Ser Cys
1 5 10 15
Leu Val Ala Ala Cys Leu Leu Leu
20

<210> 229
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<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 229
Lys Ser Ser Val Leu Val His Cys Ser Asp Gly Trp Asp Arg Thr Ala
1 5 10 15
Gln Leu Thr Ser Leu Ala Met Leu Met
20 25

<210> 230
<211> 25
<212> PRT
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<220>
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<400> 230
Gln Arg Pro Val Leu Val His Cys Ser Asp Gly Trp Asp Arg Thr Pro
1 5 10 15
Gln Ile Val Ala Leu Ala Lys Leu Leu
20 25

<210> 231
<211> 24
<212> PRT
<213> unknown

<220>
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<400> 231
Gly Cys Cys Val Ala Val His Cys Val Ala Gly Leu Gly Arg Ala Pro
1 5 10 15
Val Leu Val Ala Leu Ala Leu Ile
20

<210> 232
<211> 24
<212> PRT
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<220>
<223> Catalytic domain region

<400> 232
Gly Ser Cys Val Ala Val His Cys Val Ala Gly Leu Gly Arg Ala Pro
1 5 10 15
Val Leu Val Ala Leu Ala Leu Ile
20

<210> 233
<211> 24
<212> PRT
<213> unknown

<220>
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<400> 233
Asp Lys Leu Ile Gly Val His Cys Thr His Gly Leu Asn Arg Thr Gly
1 5 10 15
Tyr Leu Ile Cys Arg Tyr Leu Ile
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<210> 234
<211> 24
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<220>
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<400> 234
His Lys Asn Cys Val Val His Cys Met Asp Gly Arg Ala Ala Ser Ala
1 5 10 15
Val Ala Val Cys Ser Phe Leu Cys

20

<210> 235
<211> 25
<212> PRT
<213> unknown

<220>
<223> Catalytic domain region

<400> 235
Thr Lys Ser Val Leu Phe Val Cys Leu Gly Asn Ile Cys Arg Ser Pro
1 5 10 15
Ile Ala Glu Ala Val Phe Arg Lys Leu
20 25

<210> 236
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<212> PRT
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<220>
<223> Catalytic domain region

<400> 236
Glu Gly Ala Ile Ala Val His Cys Lys Ala Gly Leu Gly Arg Thr Gly
1 5 10 15
Thr Leu Ile Ala Cys Tyr Ile Met
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<210> 237
<211> 25
<212> PRT
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<220>
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<400> 237
Arg Val Ile Leu Ile Phe His Cys Glu Phe Ser Ser Glu Arg Gly Pro
1 5 10 15
Arg Met Cys Arg Phe Ile Arg Glu Arg
20 25

<210> 238
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<223> Catalytic domain region

<400> 238
His Gly Ala Thr Leu Val His Cys Ala Ala Gly Val Ser Arg Ser Ala

1 5 10 15
Thr Leu Cys Ile Ala Tyr Leu Met
20

<210> 239
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<223> Catalytic domain region

<400> 239
Gln Gly Arg Thr Leu Leu His Cys Ala Ala Gly Val Ser Arg Ser Ala
1 5 10 15
Ala Leu Cys Leu Ala Tyr Leu Met
20

<210> 240
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<220>
<223> Catalytic domain region

<400> 240
Gly Glu Ser Cys Leu Val His Cys Leu Ala Gly Val Ser Arg Ser Val
1 5 10 15
Thr Leu Val Ile Ala Tyr Ile Met
20

<210> 241
<211> 24
<212> PRT
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<220>
<223> Catalytic domain region

<400> 241
Asp Gly Val Val Leu Val His Cys Asn Ala Gly Val Ser Arg Ala Ala
1 5 10 15
Ala Ile Val Ile Gly Phe Leu Met
20

<210> 242
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<220>
<223> Catalytic domain region

<400> 242
Gly Arg Ser Val Leu Val His Cys His Ala Gly Val Ser Arg Ser Val
1 5 10 15
Ala Ile Ile Thr Ala Phe Leu Met
20

<210> 243
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<212> PRT
<213> unknown

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<400> 243
Gly Lys Cys Val Tyr Val His Cys Lys Ala Gly Arg Ser Arg Ser Ala
1 5 10 15
Thr Met Val Ala Ala Tyr Leu Ile
20

<210> 244
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<220>
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<400> 244
Thr Gly Arg Val Leu Val His Cys Ala Met Gly Val Ser Arg Ser Ala
1 5 10 15
Thr Leu Val Leu Ala Phe Leu Met
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<210> 245
<211> 24
<212> PRT
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<220>
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<400> 245
Gln Gly Leu Thr Leu Leu His Cys Met Ala Gly Val Ser Arg Ser Ala
1 5 10 15
Ser Leu Cys Leu Ala Tyr Leu Met
20

<210> 246
<211> 24
<212> PRT
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<220>

<223> Catalytic domain region

<400> 246
Gly Gly Lys Ile Leu Val His Cys Ala Val Gly Val Ser Arg Ser Ala
1 5 10 15
Thr Leu Val Leu Ala Tyr Leu Met
20

<210> 247
<211> 24
<212> PRT
<213> unknown

<220>
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<400> 247
Gly Lys Gly Leu Leu Ile His Cys Gln Ala Gly Val Ser Arg Ser Ala
1 5 10 15
Thr Ile Val Ile Ala Tyr Leu Met
20

<210> 248
<211> 24
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<220>
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<400> 248
Gly Glu Ala Val Gly Val His Cys Ala Leu Gly Phe Gly Arg Thr Gly
1 5 10 15
Thr Met Leu Ala Cys Tyr Leu Val
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<210> 249
<211> 24
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<220>
<223> Catalytic domain region

<400> 249
His Ser Lys Cys Leu Val His Cys Lys Met Gly Val Ser Arg Ser Ala
1 5 10 15
Ser Thr Val Ile Ala Tyr Ala Met
20

<210> 250
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<223> Catalytic domain region

<400> 250
Gly Ser Lys Cys Leu Val His Cys Lys Met Gly Val Ser Arg Ser Ala
1 5 10 15
Ser Thr Val Ile Ala Tyr Ala Met
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<210> 251
<211> 24
<212> PRT
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<220>
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<400> 251
His Ser Lys Ile Leu Val His Cys Val Met Gly Arg Ser Arg Ser Ala
1 5 10 15
Thr Leu Val Leu Ala Tyr Leu Met
20

<210> 252
<211> 24
<212> PRT
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<220>
<223> Catalytic domain region

<400> 252
Gly Thr His Val Leu Val His Cys Lys Met Gly Val Ser Arg Ser Ala
1 5 10 15
Ala Thr Val Leu Ala Tyr Ala Met
20

<210> 253
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<220>
<223> Catalytic domain region

<400> 253
Asn Gly Cys Val Leu Val His Cys Leu Ala Gly Ile Ser Arg Ser Ala
1 5 10 15
Thr Ile Ala Ile Ala Tyr Ile Met
20

<210> 254
<211> 24

<212> PRT
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<400> 254
Gly Ala Lys Val Leu Val His Cys Val Val Gly Val Ser Arg Ser Ala
1 5 10 15
Thr Leu Val Leu Ala Tyr Leu Met
20

<210> 255
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<220>
<223> Catalytic domain region

<400> 255
Gly Gly Asn Cys Leu Val His Cys Phe Ala Gly Ile Ser Arg Ser Thr
1 5 10 15
Thr Ile Val Thr Ala Tyr Val Met
20